

**MALIGNANT
TUMOURS OF THE VULVA**
**A Study of the Effects of Radiotherapy, Surgery
and Chemotherapy in Combination or Used Alone**

by

Ernst Simonsen



LUND 1983



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To my family, colleagues and staff
- Without their support this work
would not have been possible -

Apart from certain unpublished results the present thesis is based upon the following papers, which will be referred to in the text by their Roman numerals:

- I. Simonsen E.
INVASIVE SQUAMOUS CELL CARCINOMA IN THE VULVAR REGION.
Annales Chirurgiae et Gynaecologiae (Submitted for publication).
- II. Simonsen E, Johnsson J-E, Tropé C, Alm P and Ranstam J.
STAGE I SQUAMOUS CELL CARCINOMA OF THE VULVA.
Acta Radiologica (Accepted for publication).
- III. Simonsen E, Johnsson J-E, Tropé C and Alm P.
BASAL CELL CARCINOMA OF THE VULVA.
Obstetrics and Gynecology (Submitted for publication).
- IV. Simonsen E, Alm P, Johnsson J-E and Tropé C.
THE RECOVERY PATTERN OF PATIENTS WITH VULVAR MELANOMA TREATED BY
COMBINED SURGERY AND RADIATION THERAPY.
Annales Chirurgiae et Gynaecologiae 71:334-339, 1982.
- V. Simonsen E, Johnsson J-E and Tropé C.
RADICAL VULVECTOMY WITH WARM KNIFE- AND OPEN WOUND-TECHNIQUE IN
VULVAR MALIGNANCIES.
Gynecologic Oncology (Accepted for publication).
- VI. Simonsen E, Johnsson J-E and Tropé C.
CO₂-LASER FOR THE TREATMENT OF INVASIVE VULVAR AND VAGINAL CANCER.
Neoplasma 3/1983 (In press).
- VII. Simonsen E, Nordberg U-B, Johnsson J-E, Lamm I-L and Tropé C.
RADIOTHERAPY AND SURGERY IN THE TREATMENT OF REGIONAL LYMPH NODES
IN SQUAMOUS CELL CARCINOMA OF THE VULVA.
Acta Radiologica (Submitted for publication).
- VIII. Tropé C, Johnsson J-E, Larsson G and Simonsen E.
BLEOMYCINE ALONE OR COMBINED WITH MITOMYCIN C IN TREATMENT OF
ADVANCED OR RECURRENT SQUAMOUS CELL CARCINOMA OF THE VULVA.
Cancer Treatment Reports 64:639-642, 1980.

IX. Simonsen E.

TREATMENT OF RECURRENT SQUAMOUS CELL CARCINOMA OF THE VULVA.

Acta Radiologica (Accepted for publication).

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INTRODUCTION

In the past, the successful treatment of malignant affections of the vulva has become an increasingly difficult problem requiring the utmost clinical acumen and surgical skill. The surgical treatment of this group of patients, at advanced age and therefore, as a rule, also suffering from some geriatric degenerative disease, was a difficult and often hopeless task.

The early literature concerning malignant disease of the vulva has not been systematically, and it is not easy to establish when the disease was first described. The first recorded reference was made by the anatomist John Baptist Morgagni in 1751. He vaguely mentioned the disease, but stated, "but as to those that relate to penis, anus and genital parts of women, although I have seen many of these, yet as I have never had any opportunity of dissecting them, there is scarcely anything for me to hint at". Louis Mayers in 1866 was the first with a clinical publication, in which he reviewed the literature since 1839, containing 28 cases. The nineteenth century literature contains many references to vulvar carcinoma, most of them single case reports.

Carcinoma of the vulva has presented one of the most obstinate therapeutic problems in medical science. Up to the end of the 19th century, treatment of vulvar cancer consisted of local excision or cautery, but no lymphadenectomy. As recently as 1939, the world-wide healing rate was on an average only about 15 %.

Increased knowledge about lymphatic metastases gave impetus to therapeutic efforts. Virchow's theory that a metastasis issued from the tissue of the lymph nodes prevailed up to the middle of the 19th century (Lundwall 1961).

Gussenbauer (1881) advanced a theory of pure transport by embolism of young cells from the tumour, which were not actual tumour cells. He found microscopical evidence of cancer in the regional lymph nodes. Rupprecht (1886) published a paper on dissection of the inguinal regions, which he had performed in 18 patients. A really important publication was that of Basset in his Graduation Thesis in 1912, which led to the definition of radical operation, the modern treatment of the disease. The operation was originally intended only for treatment of carcinoma of the clitoris, and the vulvectomy was to be partial, comprising only the anterior part of the vulva. He formulated the following two principles: 1) A carcinoma must be excised in a way as radical as possible, at an ample distance from its presumed limits.

2) Whenever possible, it is desirable to dissect the entire lymphatic system which drains the region of the tumour, and, furthermore, the lymph nodes, which constitute the first station in the system.

Basset's procedure was popularised in America by Taussig (1917). He put the operation into practice in 1915. He published a large series of radical operations according to Basset's principles in 1940, with a five-year survival rate of 52.6 % in node-involved cases. A standardization of the method was introduced in 1941 by Way (1948). He brought about the radical change in treatment from the pioneering efforts of the late 19th century of the enlightened attitude of the 20th century.

At the beginning of this century, however, radium therapy was the method of choice. This therapy has been carried out with different methods. Direct treatment of the tumour with contact therapy was used by Forssell (1914), radium moulds by Berven (1949), and implantations of radium needles around the tumour by Stoeckel (1930) and Friedman (1932). This treatment was not effective, and the results very discouraging, with a healing frequency of 10-20 %. The radium mould and the radium contact therapy were rather ineffective due to the dose gradient. The necessary tumour dose achieved with radium needles often gave severe and very painful radiation reactions and necrosis. Lundwall (1961) treated the primary tumour with irradiation; the radiation parameters were 100-180 kV, SSD: 40-50 cm, and single-field technique. The peak absorbed dose per fraction was 50-200 rad. A total of 1450-7250 rad was given with a calculated absorbed dose at a depth of 2 cm of 1260-6670 rad.

The use of radium needles implanted in the regional lymph nodes and along the lymphatics as the only treatment of the groins or in combination with a later groin dissection, was described by Stoeckel (1930) and Friedman (1932). "Teleradium" therapy was reported by Berven (1949) in the treatment of the groins. The calculated absorbed dose at a depth of 3 cm was 45 % of the peak absorbed dose. Each groin was divided into two fields with a diameter of 5 cm. The peak absorbed dose was 900 rad per fraction, three-to-four fractions in each field. A total of 2700-3600 rad was given. Ninety-six patients with clinically established groin metastases were treated according to this schedule. Twenty-eight of these underwent subsequent operation. The 5-year survival was 22 %.

Ellis (1949) and Lundwall (1961), among others, have described irradiation treatment with conventional X-ray irradiation of the tumour of the groins or of both. Lundwall (1961) used a peak absorbed dose of 1040-6010 rad in the treatment of the groin regions. The calculated dose at a depth of 2 cm was 960-5640 rad, and at a depth of 5 cm it was 710-4270 rad, with the same radiation parameters as for the primary tumour. He concluded that the results of radiotherapy were inferior to those of radical surgery. The radiation reaction is extremely pronounced, and a sufficient dose to the tumour is not obtainable without more or less prolonged and painful radiation damage. Stoeckel (1930) published a review of the literature evaluating radium therapy alone in 126 patients with only 11.9 % healing. After the publications from Taussig and Way, with more than 50 % 5-year survival when using Basset's procedure in relation to the poor survival figures with the radium therapy, most centres, especially in the USA and Great Britain, concluded that irradiation did not have any place in the treatment of vulvar malignancies. In some centres in Europe, the irradiation was, however, used in combination with radical surgery as pre- or postoperative treatment of the primary tumour (Berven 1949) or the groins (Fochem 1957, Edsmyr 1962).

S. Way stated that the survival was directly related to a wide and deep removal of the vulva coupled with an aggressive attack on the regional lymph nodes. His treatment model has been the treatment of choice in most centres the last 30-40 years. During these years, many reports have nevertheless described modifications on Way's technique. Locally advanced diseases represent a difficult management problem. Brunschwig and Daniel (1956) introduced pelvic exenterations as an alternative for treating advanced carcinoma of the vulva.

Postoperative complications and operative mortality are often proportional to the aggressiveness of the surgical approach. In an attempt to reduce operative and postoperative complications, various modifications of the surgical technique have been introduced. A modification of the classical line of incision is described by Abitbol (1973). Open wound technique was used by Daly (1979). Improved radiation therapy technique during the last decades have enabled irradiation with more adequate dose distributions and less complications. These techniques have actualised irradiation in combination with surgery.

Preoperative radiation therapy prior to radical surgery has been described by Acosta (1978) and Boronow (1982). Radical vulvectomy followed by irradi-

ation of the lymph node stations without surgical node dissection has been described by Daly (1974), Weghaupt (1978), Kucera (1980) and Frankendahl (1973).

Combined treatment with preoperative irradiation and surgery as an alternative to exenteration in local advanced vulvar cancer was described by Boronow (1982), and with pre- and postoperative irradiation by Hamberger (1978) and by Jafari (1981). In the series reported by Jafari, good results are shown in a number of patients treated only with irradiation.

In Europe, the very aggressive surgical approach, with its high morbidity and mortality rates, has not been accepted by all centres. Radical electrocoagulation of the entire vulvar area was described by Berven (1941), and this method has, with modifications, been used in several centres. This method, combined with radiation of the lymph node stations in the groin and pelvic regions, with or without surgical lymphadenectomy of the groin and pelvic nodes, has resulted in acceptable 5-year survival rates, with low morbidity and mortality in connection with the treatment (Edsmyr 1962).

INCIDENCE AND AGE

Malignant tumour in the vulvar region is the fourth most common gynecological malignant disease (~5 %), after carcinoma of the ovary, the uterine body and the uterine cervix. The most common vulvar malignancy is squamous cell carcinoma. In material from various parts of the world, invasive squamous cell carcinoma has been reported to constitute about 90 % of vulvar malignancies. The second most common vulvar malignancy is malignant melanoma (5-8 %), and the third most common is basal cell carcinoma (2-3 %). Rare types of vulvar malignancies, such as adenocarcinoma, adeno-acanthoma and lymphoma, as well as mesodermal tumours, in the form of leiomyosarcoma, myoblastoma and fibrosarcoma, have been reported.

Cancer incidence rates per 100 000

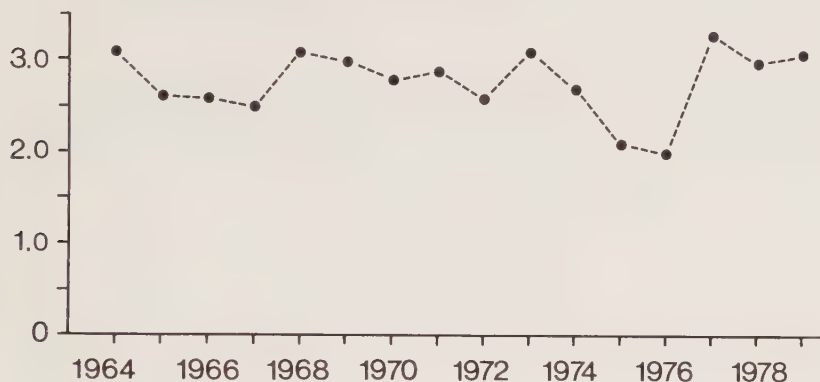


Fig 1. Annual vulvar cancer incidence rates per 100 000 in Sweden.

Recent reports show a considerable increase in the incidence of vulvar squamous cell carcinoma during the last 25 years. Andreasson (1980) shows a ten-fold increase in the number of cases of invasive vulvar carcinoma recorded from 1950 to 1975 in Denmark. Other investigators have reported the same tendency (Green 1978). There is no record of significant increase during the last 25 years in Sweden (Fig 1), but, on the other hand, the Swedish and Danish incidence rates per 100 000 women are nearly identical today. It is impossible to estimate the actual incidence of cancer of the vulva. Worldwide, many countries do not publish any figures, and no discrimination is made between carcinoma of the vulva and of the vagina.

AIMS OF THE PRESENT STUDY

The major problem in the successful management of malignant lesions of the vulva is early diagnosis and radical surgery, avoiding high rates of treatment complications. The aims of the present report are to give directions in regard to the solution of this problem, by evaluating:

1. The treatment results obtained in 317 consecutive cases of vulvar malignancies during the 20-year period between 1960-1979.
2. The effect of surgery in primary treatment and in treatment of recurrences.
3. The effect of radiotherapy in primary treatment and in treatment of recurrences.
4. The effect of chemotherapy in advanced and recurrent squamous cell carcinoma of the vulva.
5. The possibility to optimise the treatment techniques and reduce the treatment complications, with individualisation of the treatment approach, based on classification and histological examination of the tumour specimens.

MATERIAL

During the 20-year period between 1960-1979, 317 patients with vulvar malignancies were treated at the Gynecologic Section, Department of Oncology, University Hospital in Lund.

Table I. Histopathological findings in the 317 patients with vulvar tumours. The youngest treated patient was 16 years old, and the oldest 96, the mean age was 70.

Histology	No. of patients
Squamous cell carcinoma	266
well differentiated	183
moderately differentiated	62
poorly differentiated	21
Malignant melanoma	25
Basal cell carcinoma	14
Morbus Paget	4
Anaplastic carcinoma	2
Adenocarcinoma	2
Adenosquamous carcinoma	1
Lymphoma	1
Rhabdomyosarcoma	1
Leiomyosarcoma	1
Total	317

Classification

Table II. TNM system (UICC).

T	Primary tumour
T ₁	Tumour confined to vulva - 2 cm or less in diameter
T ₂	Tumour confined to vulva - more than 2 cm in diameter
T ₃	Tumour of any size with adjacent spread to the urethra and/or perineum, and/or to the anus
T ₄	Tumour of any size infiltrating to bladder mucosa and/or the rectal mucosa or both, including the upper part of the urethral mucosa and/or fixed to the bone
N	Regional lymph nodes
N ₀	No nodes palpable
N ₁	Nodes palpable in either groin not enlarged mobile (not clinically suspicious of neoplasm)
N ₂	Nodes palpable in either one or both groins enlarged, firm and mobile (clinically suspicious of neoplasm)
N ₃	Fixed or ulcerated nodes
M	Distant metastases
M ₀	No clinical metastases
M ₁	(a) palpable deep pelvic nodes
M ₁	(b) other distant metastases

Table III. FIGO classification according to the TNM system.

Stage I	T ₁	N ₀	M ₀
	T ₁	N ₁	M ₀
Stage II	T ₂	N ₀	M ₀
	T ₂	N ₁	M ₀
Stage III	T ₃	N ₀	M ₀
	T ₃	N ₁	M ₀
	T ₃	N ₂	M ₀
	T ₁	N ₂	M ₀
	T ₂	N ₂	M ₀
Stage IV	T ₁	N ₃	M ₀
	T ₂	N ₃	M ₀
	T ₃	N ₃	M ₀
	T ₄	N ₃	M ₀
	T ₄	N ₀	M ₀
	T ₄	N ₁	M ₀
	T ₄	N ₂	M ₀
and all others with M ₁ (a) and M ₁ (b)			

All patients were classified after the TNM system (UICC) and staged according to the FIGO system (Tables II-VI).

Table IV. Distribution of stage (FIGO).

	Stage I	Stage II	Stage III	Stage IV
Squamous cell carcinoma	86	67	76	37
Malignant melanoma	9	4	4	4
Basal cell carcinoma	12	6	-	-

Table V. Distribution of primary tumour size, TNM system (UICC).

	T ₁	T ₂	T ₃	T ₄
Squamous cell carcinoma	102	99	55	10
Malignant melanoma	14	7	4	-
Basal cell carcinoma	12	6	-	-

Table VI. Distribution of the clinical evaluation of regional lymph nodes according to the TNM system (UICC).

	N ₀	N ₁	N ₂	N ₃
Squamous cell carcinoma	150	22	64	30
Malignant melanoma	16	2	5	2
Basal cell carcinoma	16	2	-	-

Squamous cell carcinoma (Reports I, II, VII, IX): (Report I) During the years 1960-1979, 266 patients with squamous cell carcinoma were treated in the department. This material was used to analyse the prognostic factors of squamous cell carcinoma. The mean age was 68 years (range 16-96), and the median age was 70.

(Report II) Eighty-six patients had stage I (FIGO) disease. For these patients, the operative specimens were re-examined and classified by the same pathologist. The degree of differentiation (well, moderately or poorly differentiated) was based on the least differentiated elements in the specimens (Ackerman 1947). In 77 patients, the future prognoses were estimated from properties of the tumour cell population: structure, differentiation into cell type, nuclear polymorphism and mitosis, and the tumour host relationship: mode of invasion, stage of invasion, vascular invasion and (lymphatic) cellular response, which were graded according to a point-score system used for squamous cell carcinoma of the larynx (Jakobsson 1973, Jakobsson et coll 1973), the palate (Eneroth & Moberger 1973), the gingiva (Willén et coll 1975), the uterine cervix (Stendahl et coll 1979) and the vulva (Kabulski & Frankman 1978). Each parameter was given 1-to-3 points resulting in a total of 8-to-24 points with increasing grade of malignancy. The total point-score values were compared with 5-year crude survival to

find out whether the point-score system could be used for prognostic purposes in stage I vulvar squamous cell carcinomas.

(Report VII) The treatment of the regional lymph node stations has been a combination of surgery and irradiation, or irradiation alone. These treatments have been analysed in a material of patients with squamous cell carcinoma treated during the years 1962-1979. During the period 1960-1961, our treatment technique was different from that used later on. One-hundred-sixty patients were (N_0 - N_1) and 84 patients were (N_2 - N_3) (UICC).

(Report IX) Two-hundred-forty-four patients of the group of 266 patients with squamous cell carcinoma were given treatment with curative intention. Of these patients, 60 had developed local and/or regional treatment failures. The treatment for these patients consisted of surgery, irradiation or chemotherapy, or in combination.

Malignant melanoma (Report IV): During the years 1960-1979, 25 patients with malignant melanoma were treated. The biopsies and surgical specimens for the patients with malignant melanoma were histopathologically re-examined, and classification was performed according to Clark (1969). Clark's system is based on the inverse relationship between survival rates and the level of infiltration in cases of cutaneous melanomas. Tumour infiltration is classified in the following manner:

- Level I Tumour cells confined to the epidermis.
- Level II Tumour cells extending into the papillary portion of the dermis.
- Level III Tumour cells filling the papillary dermis and "pushing" down upon the reticular dermis.
- Level IV Tumour cells extending into the reticular dermis.
- Level V Tumour cells extending into the subcutis.

This material was used to analyse the prognostic factors of malignant melanoma. The mean age in the group was 67 years (range 36-86).

Basal cell carcinoma (Report III): During the years 1960-1979, 21 patients (including five treated outside the department) had received the histological diagnosis of basal cell carcinoma. In three patients, however, mixed tumour was recorded. This material was used to analyse the prognostic factors of basal cell carcinoma. The median and mean ages were 79.5 and 76, respectively (range 55-90).

(Report V) The treatment of the primary local tumour has been radical vulvectomy. Of 317 patients, this operation was done in 274. Forty-three patients were excluded from this study. Twenty-five received only palliative treatment, due to old age, poor general condition and advanced disease. Fifteen patients with the diagnosis basal cell carcinoma or extremely early squamous cell carcinoma underwent partial vulvectomy. Three patients refused treatment. The evaluation of the surgical method is based on these 274 patients.

(Report VI) During the period 1980-1981, a new operation technique, laser-beam scalpel, was used in a series of 21 patients, including seven primary and six recurrent vulvar carcinomas, five vaginal carcinomas, one urethral carcinoma and two pre-invasive vulvar carcinomas.

(Report VIII) During the period 1978-1979, two patients with primarily advanced cancer of the vulva and 18 with recurrent and/or distant metastatic cancer of the vulva were treated with chemotherapy. All of these 20 patients had squamous cell carcinoma.

METHODS

Treatment

The same treatment principles have been used during the last 20-year period. The patients have been treated with combined surgery and radiation therapy. Chemotherapy has only been used as palliative procedure, or in combination with surgery and radiotherapy in cases of treatment failure.

Surgery

Radical vulvectomy using warm knife- and open wound-technique was performed as the first step in the two-phase surgical approach. Using warm knife technique, the vulva was removed with its underlying subcutaneous tissues and muscles. The medial limit of the dissection was the hymenal ring, leaving the urethra intact. The lateral limit was the labio-crural fold, crossing the perineum above the anus caudally and mons veneris cranially, and the intended minimal free margin to the tumour was 2 cm. Individualization of resection line, however, was sometimes necessary in the patient material studied here, because of the localisation and extent of the tumour. The excision was done to the deep fascia. Excision of parts of the urogenital diaphragma and the distal part of the urethra, as well as dissection of paravaginal and ischorectal spaces, were sometimes done, as well. After removal of the operation specimen, the wound surfaces were diathermically coagulated, partly to stop the bleeding and partly to destroy the tumour cells eventually left in the operation area. The wound was left open for secondary healing.

A Dextran solution with penicillin and boracic vaseline were applied alternatively during the initial ten days for the treatment of the local wound, after which time only boracic vaseline was used. An indwelling catheter was installed for 3-5 days.

Lymphadenectomy was performed six weeks later if the general condition of the patient so permitted. The lymphadenectomy was generally formed as bilateral inguinal lymphadenectomy. Pelvic lymphadenectomy was performed in cases where a clinical preoperative examination revealed metastasis in the inguinal lymph node stations. The surgical technique for inguinal lymphadenectomy includes dissection of the inguinal nodes, stripping of the femoral vessels and the deep fascia from muscles. With pelvic lymphadenectomy, the inguinal ligament is, as a rule, not split, and the perineum is swept medially to expose the external iliac vessels up to the bifurcation of the common iliac vessels, in order to allow removal of the interiliac lymph nodes, as well. These surgical principles have changed only moderately during the 20-year period of the study.

Only few cases necessitated a deviation from the two-step procedure, and if so, only in relatively advanced cases, where the inguinal lymph nodes were initially found with clinically manifest metastasis. Inguinal lymphadenectomy is in principle always carried out bilaterally, except in cases where, during operation of the primary side, it was determined that radical surgery could not be performed, and surgical treatment on the other side was then abandoned.

Radiotherapy

External irradiation has been given to the local tumours in advanced cases, in order to make them operable. Surgery, if possible, was performed about 6 weeks after conclusion of this treatment. Single-field technique was used, and a peak absorbed dose of 3 Gy per fraction, three fractions a week, to a total of 24–51 Gy. Depending on the calculated depth of the tumour infiltration, the tumour size and site, photons from a ^{137}Cs -unit, a ^{60}Co -unit or 15–35 MeV electrons were used.

Preoperative irradiation of the groin region has been given in connection with the vulvar surgery, six weeks prior to lymphadenectomy. During 1960–1961, a decacurie-unit was used for this preoperative treatment. From 1962 to 1979, a ^{137}Cs -unit was used with single-field technique, a field size of 8 x 13 cm and SSD 20 cm. The peak absorbed dose was 7 Gy per fraction. Three fractions a week up to a total of 21 Gy were given. The deepest part of the target, representing the inguinal nodes, was assumed to be located 3 cm below the skin surface. This will give a target absorbed dose (specification point on the central axis at the centre of the target area) of 17.6 Gy.

When metastatic nodes were detected microscopically in the surgical specimens, the inguinal region and the pelvic nodes on the side in question were given postoperative external irradiation, as a rule using a ^{60}Co -unit with single-field technique, SSD 80 cm and a field size of about 150 cm². The peak absorbed dose was 3 Gy per fraction, five fractions a week up to a total peak absorbed dose of about 24 Gy to about 33 Gy, respectively, depending on the findings in the surgical specimens (metastatic growth in the nodes only or metastatic growth outside the nodes). The deepest part of the target, representing the operation area and the external and interiliac lymph nodes, was assumed to be located 10 cm from the skin surface. The target absorbed dose (specification point on the central axis at the centre of the target area) was 9.6 Gy to 33.6 Gy, respectively.

The radiotherapeutic technique has been improved and the standard target volumes have been changed during the 20-year period. Patients not operated with lymphadenectomy have been given radiotherapy of the groins with a total absorbed dose from 17.6 to 42.8 Gy.

Chemotherapy

The chemotherapy used was bleomycin or bleomycin in combination with mitomycin C. The bleomycin regimen used was 15 mg i m twice a week up to a total dose of ≤ 300 mg. The combination bleomycin-mitomycin C regimen used was: bleomycin 5 mg i v during 6-8 hours on days 1-7 and mitomycin C 10 mg i v on day 8 as a bolus dose. This dose schedule was given as one course repeated four times, with a 1-week recession period between each course.

Most patients were followed up at the department for a minimum of 10 years after initial treatment. Only about 5 % were checked in their local hospital. No patient had incomplete follow-up. The observation time was from 2-to-20 years.

Statistical methods

Survival calculations and statistical analysis were made using the life table technique of Peto (1977) and the Cox multivariate analysis by Cox's proportional hazards model, as described by Kalbfleisch (1980).

RESULTS

Treatment

Radical vulvectomy: Treatment of the primary tumour (Reports V, VI)
Radical vulvectomy using warm knife technique has, as a rule, been performed. This operation was done on 274 patients. There was no record of deaths during operation or postoperative care. The mean hospitalization period for vulvectomy was 16 days.

The patients suffered no pain in the wound during the first 3-to-4 days. Normal wound pain was registered in the following period. The patients were fully mobilized the day after the operation, and, as a rule, no parenteral nutrition was necessary. Wound healing with secondary granulations was completed within 6-8 weeks. Postoperative bleeding of $>\frac{1}{2}$ l was registered in nine cases. Wound infection necessitating administration of antibiotics occurred in nine patients. In two, extensive necrosis of the operation area was seen. One case of pubic osteitis, which in less than six weeks responded to antibiotic treatment and left no permanent injury, was registered. Incontinence was found in one case, where resection of almost half of the urethra was performed in connection with the vulvectomy. Vulvar stricture was frequent following vulvectomy. In twelve patients, this caused complaints necessitating correction of the stricture. Five patients suffered from prolapsus following the operation. One postoperative case of vesicovaginal fistula was reported. Four thromboses of the lower extremities and one pulmonary emboli were observed.

The surgical radicality was less pronounced in cases with extensive tumour growths and tumour infiltration in extra-vulvar tissue.

Sixty-three (23 %) local treatment failures have been recorded, progressive disease (treatment failures within 6 months) in 21 patients and local recurrences in 42. Non-radical, initial surgery was performed in 20/63 patients (32 %), and 13/63 (21 %) were given surgery of dubious radicality. In 3/63 local treatment failures were localized in the skin-bridge between the vulva and the groin area. For patients with local recurrences and local progressive disease, the prognosis was poor. 16/20 patients not radically operated, 10/13 operated with dubious radicality and 12/30 patients radically operated died of the disease within five years.

Of 223 patients with a minimum of 5 years' observation, 67 died of their disease and 23 patients died of intercurrent disease. The crude 5-year survival was 60 %.

Laser-beam surgery: In an attempt to improve the operation technique, a laser-beam scalpel was used in a series of 21 patients. All of the operative specimens were radically excised. The examination of the specimens was uncomplicated due to insignificant degrees of tissue necrosis at the edges.

The bleeding and healing process at surgery was about the same with both laser-beam scalpel and with electrosurgical scalpel using open wound technique. The surgical time was longer with the laser technique, but the operative specimens were better preserved. Healing of the primary closed wounds was uncomplicated.

Treatment of the regional lymph node stations (Reports I, VII) has been carried out as a combined treatment with radiotherapy and surgery or as radiotherapy alone.

Metastatic lymph nodes indicate a poor prognosis. In a series of 266 patients (Report I) with squamous cell carcinoma, the 5-year survival rates for patients who underwent lymphadenectomy (122) were 40 % for patients with metastatic nodes (62 patients) and 82 % for patients with non-metastatic nodes (60 patients).

In the group of patients with squamous cell carcinoma (244 patients) treated from 1962-1979 with combined surgery and irradiation alone (Report VII), groin lymphadenectomy was performed in 114 cases and pelvic lymphadenectomy in 24 cases.

Seventy of 160 patients without clinical suspicion of lymph node metastases (N_0-N_1) in the groins were operated with groin lymphadenectomy, of whom 24 (34 %) had metastases in the regional lymph node stations. Two of eight with pelvic lymphadenectomy had metastases in the pelvic lymph nodes.

Forty-four of 84 patients with clinically manifest or suspected lymph node metastases (N_2-N_3) were operated with groin lymphadenectomy. Metastases were found in the regional lymph nodes in 34 of these 44 patients. Of the sixteen patients submitted to pelvic lymphadenectomy metastases were found in ten.

Seven cases of regional treatment failures were recorded in the 24 patients in whom pelvic lymphadenectomy was performed. All seven cases were localized in both the inguinal and pelvic nodes.

Regional metastases occurred in 19 of the 87 patients who only had groin dis-

section (three patients not given preoperative radiotherapy excluded). In 15 of these patients, the metastasizing was adjudged as either occurring in the pelvic lymph nodes (in four cases) or both in the pelvic lymph nodes and in the inguinal surgical area; only four patients had metastases solely in the inguinal surgical area. Nineteen (20 %) of the 97 patients who were only treated with irradiation of the regional lymph node stations later got regional metastases. Ten of these cases were adjudged as located in the pelvic lymph nodes.

No cases of leg edema or thrombosis were recorded among the patients who were only treated with irradiation of the inguinal regions. Leg edema was found in 5/24 (~21 %) of the patients who received pelvic lymphadenectomy; the corresponding figure for the patients who only received groin dissection was 12/90 (13 %). Thrombosis occurred in 7/114 (6 %) patients, of whom three also showed symptoms of pulmonary embolism. Infected wounds requiring treatment were recorded in 12/114 (11 %) patients. No cases of skin necrosis were observed. There was no per- or postoperative mortality.

Basal cell carcinoma (Report III): Twenty-one patients with basal cell carcinoma are reviewed. No cases of pure basal cell carcinoma gave metastases to the regional lymph nodes; in no case could the cause of death be considered directly attributable to this kind of lesion. Squamous elements in basal cell carcinoma occur relatively frequently; this is a benign phenomenon with no effect on the prognosis.

Double carcinomas, with malignant melanoma or squamous cell carcinoma growing in close proximity to the basal cell carcinoma, occur frequently. These double carcinomas are to be treated as prescribed for the most aggressive types of tumour, since the prognosis follows their pattern.

Malignant melanoma (Report IV): Twenty-five patients with malignant melanoma are reviewed. Crude five-year survival was 9/21 (43 %). Patients with tumours in Clark levels II-IV have been found to have a good prognosis (7/9), while those with Clark V-tumours have had an extremely poor prognosis (2/10). If Clark classification and radical surgery are used as the basis for a prognostic selection method, only one out of eight patients classified as Clark II-IV died of the disease within five years. Of the patients classified as Clark V and who underwent similar surgery, six out of eight died within five years. Prophylactic dissection of the inguinal nodes has not been found to improve the prognosis (all of the four patients who had involvement of the inguinal lymph nodes died within two years) and pelvic lymphadenectomy is not con-

sidered to be advisable. Six of the eight patients with involvement of the clitoris died from their disease within five years following treatment.

Squamous cell carcinoma (Reports I, II): Two-hundred-sixty-six patients with squamous cell carcinoma are reviewed. No per- or postoperative mortality was observed in this material. The mean hospitalization time for vulvectomies as well as for lymphadenectomies has been 16 days.

The metastatic incidence increases from T₁ to T₄ tumours. Of a total of 122 patients who underwent lymphadenectomy, 62 (51 %) had metastases in the lymph nodes. Among the 26 patients who underwent dissection of the pelvic nodes, 12 (46 %) had metastases in the pelvic lymph nodes. Involved inguinal nodes on the same side were found in all of these patients.

Five-year crude survival rate could be calculated in 211 out of 266 patients with squamous cell carcinoma, the five-year crude survival was 59 % for those 195 patients who underwent surgery with curative intention, the corresponding figure was 64 %.

Moderately and poorly differentiated tumours had non-significantly poorer prognoses than well differentiated ones.

In the 76 out of 86 patients with stage I tumours, for whom five-year survival could be calculated, six succumbed from the cancer disease and seven patients expired from intercurrent disease. The five-year crude survival was 81 %. No differences were seen in the frequencies of tumour recurrences and metastases between groups with different tumour differentiation. From the point-score values it was, furthermore, not possible to divide the material into various patient groups with different prognoses. There was, however, a positive correlation between local recurrences and scoring values (p 0.03). Multivariate analysis of the different parameters used in the point-score analyses showed the mode of invasion to be the most important one (p 0.001). Six local recurrences (~12 %) were reported among the 49 patients with a score of one point and ten local recurrences (~30 %) where the patient had a score of at least two points. Among the seven patients with lymph node metastases, the separate point-score value for vascular invasion was at least two points (implying a high suspicion of vascular invasion).

Treatment failures (Report IX): Of the 244 patients who underwent curative treatment failures (local recurrence, regional or distant metastasis)

appeared within 6 months after primary treatment in 19 cases. Treatment failures appearing more than 6 months after primary treatment occurred as local recurrences in 29 patients, and as regional or distant metastases in 15 patients.

Twenty-five per cent of the patients developed treatment failures from 0-16 years after primary treatment. Ninety per cent of the failures were diagnosed within 2 years after primary treatment. The recurrence incidence increases and the time interval is shorter in relation to increasing tumour size. As reported by others, extremely few recurrences were recorded with tumour size of less than one cm in diameter. Early local recurrences have a poor prognosis and often occur in patients not receiving radical surgery. Regional metastases always have a poor prognosis.

Surgery, chemotherapy, and irradiation have been used to treat treatment failures. A combination of treatment modalities is commonly used. Relapse has occurred in several patients. Only 20 % of the patients treated for recurrences and metastases are alive five years after their first relapse.

GENERAL DISCUSSION

The present treatment model with a combination of radiotherapy and surgery has given results comparable with those reported from other centres in the last decades (Das Gupta 1964, Franklin 1971, Wharton 1974, Chung 1975, Morely 1976, Morrow 1976, Green 1978, Benedet 1979, Stening 1980, Andreasson 1980, Iversen 1981).

In this series, the frequency of postoperative complications is low and there is an operative mortality of less than 1 %. Our operation time is very short, and the postoperative hospitalization time is only 16 days on the average. No important disadvantages with the warm knife- and open wound-technique using 2-seance surgery have been found. The treatment results and the low frequency of postoperative complications and operative mortality are to be considered in relation to the high rates of wound break-down, local sépsis, prolonged hospital stays, pelvic relaxation and operative mortality, that have accompanied the aggressive surgical approaches practiced in most other centres. An operation time of approximately 4-5 hours or more is normal (House 1968, Karlen 1975). Wound infection and dehiscence have been reported as rates that vary from 20 to nearly 60 % (Morgan 1980). Postoperative hospital stays of 40-60 days are not uncommon (Way 1978, Andreasson 1980). Pelvic relaxation is a long-term complication with an incidence of 4-24 % (Calame 1980). Operative mortality is parallel to the aggressivity of the surgical approach. At radical vulvectomy, it is 1-3 % (Brunschwig 1967), at radical vulvectomy and groin lymphadenectomy it is 5-10 % (Andreasson 1980, Iversen 1981), and at pelvic exenteration it is 6-25 % (Brunschwig 1967, Karlen 1975, Rutledge 1977). Postoperative complications are so common that when they do not occur, this has sometimes been considered indicative of incomplete operation.

The CO₂-laser-beam technique has shown no important advantage over the warm knife-technique for surgery with radical vulvectomy. For local extirpation of small tumours, such as basal cell carcinoma and benign tumours, and in cases with microinvasive squamous cell carcinoma (T₁), the laser-beam technique can be preferable.

The frequency of locally non-radical surgical intervention is too high in our series. This fact is more a question of a surgical approach lacking in aggressiveness than of a limitation of the surgical method we have used. The frequency of recurrences and the survival have a direct relation to the surgical radicality. It is therefore very important to emphasize that

surgical radicality is mandatory in the treatment of these malignancies. If the primary surgery proves to be non-radical or dubiously radical, the recommendation must be a new operation, if this is possible.

Surgical attack against the pelvine retroperitoneal lymph nodes is a very controversial question (Friedrich 1976, Morely 1981). In nearly all reports, the prognosis is stated to be very poor if the pelvine lymph nodes are involved at the time for primary treatment. In the present series, three out of eleven patients with metastases in the pelvine lymph nodes survived more than five years, but the material is too limited to allow any definite conclusions. Metastatic lymph nodes on the pelvic wall are almost never seen without metastatic lymph nodes in the groin region on the same side. S. Way has in nearly all of his earlier reports described pelvic lymph node metastases without metastatic lymph nodes in the groin region, but in his report from 1982, he has changed his earlier opinion. Pelvic lymphadenectomy is never indicated if no metastatic lymph nodes are found in the groin region. In the present series, no cases of contralateral metastatic lymph nodes without ipsilateral metastatic lymph nodes have been seen, in cases of one-sided tumours. If no ipsilateral lymph node metastases are found, no operation on the contralateral side is thus indicated. In the literature (Karlsgren 1977, Morris 1977, Iversen 1981, Neville 1983), this is an accepted opinion in cases with stage I tumours, but in cases with stages II-IV tumours there are different viewpoints (Way 1960, Edsmyr 1962). In cases with malignant melanomas, prophylactic inguinal lymphadenectomy has not been found to improve the prognosis (Morrow 1972, Olsen 1981), and pelvic lymphadenectomy is not considered to be advisable. In patients with confirmed regional or distant metastases, there were no cases of successful cure.

In cases with basal cell carcinoma, there is no need for lymphadenectomy, since basal cell carcinoma never or rarely metastasizes.

The methods of selection, histological differentiation of tumours (well, moderate, poor), and the scoring-system (tumour cell population and tumour host relationship) used in the study of squamous cell carcinoma do not allow working out differentiated treatment schemes at the present stage. Multivariate analysis of the different parameters used in the scoring for stage I squamous cell carcinoma nevertheless showed that the "mode of invasion" was an important prognostic factor ($p < 0.001$). The histopathologic examination also showed that stage I tumours with very low score never developed metastases and in no case caused the death of the patient. Kabulski and

Frankman (1978) showed in their report that tumours with a high score had a poor prognosis. We could not confirm their assertion, but the explanation might be that we have only examined stage I carcinomas with a generally good prognosis, whereas Kabulski and Frankman studied 40 patients in stages I and II (stage I, 19 and stage II, 21). In their material, only three patients with stage I disease died of cancer, but of the patients with stage II, nine died in cancer.

Other investigators who have attempted to use histological grading of malignancy (Wharton 1974, Parker 1975, Buschema 1980, Buschema 1981, Chu 1981, Iversen 1981, Andreasson 1982) have shown that tumour infiltration of more than 3-5 mm in depth and tumour growth in vessels are important prognostic factors. Further investigations with histopathologic grading systems may lead to evaluation in groups with more or less biologically aggressive behaviour of the carcinoma, as is seen with squamous cell carcinoma in the cervix uteri (Stendahl 1981). A histological scoring-system for preoperative biopsies can be a help for working out more differentiated treatment models in the future.

The Clark classification has been used for histological staging of malignant melanomas. The correlation between prognosis and the Clark level has shown that Clark V-tumours have a clearly poor prognosis, but the Clark classification cannot form the basis for differentiating the aggressiveness of treatment. For this aggressive tumour disease, an aggressive surgical approach must be the treatment of choice in any case.

It is very difficult to clinically evaluate tumour growth in the inguinal lymph nodes. Most reports in the literature state that, at groin dissection, metastases were found in 16-39 % of patients considered to have normal lymph nodes (Lundwall 1961, Plentle 1971, Daly 1974, Iversen 1981, Way 1982). This agrees well with our experience (34 %). It is possible that the routine use of fine needle biopsy would improve the preoperative evaluation of the patient. Histopathological microscopic examination of the excised lymph nodes should always be done peroperatively at lymphadenectomy. As these patients are usually of advanced age, the vulvectomy, which they tolerate relatively well, can be utilized to see if lymphadenectomy can be carried out as planned. If this is not considered advisable, the "preoperative" irradiation can be the first series of solely irradiative treatment of the regional lymph node stations.

The less aggressive radiation therapy of the groins that has been used in this material is not sufficient as the sole treatment of the lymph nodes. A more consequent planning, with one treatment program for patients to be given a combined radiological and surgical treatment of the groin lymph nodes, and another treatment program, where only radiation therapy of the lymph nodes is planned, must be the best recommendation. The photon energy (γ -radiation from a ^{137}Cs -unit) with single-field technique used preoperatively gives a variation of the absorbed radiation dose in the primary target (i.e. the inguinal lymph node stations) of $\pm 17\%$, which is acceptable. The radiation dose is, however, rather low in view of the treatment volume, which contains no critical organs. Gamma-radiation from a ^{60}Co -unit with single-field technique has as a rule been used for treating the secondary target (the external and interiliac lymph nodes), and the total target postoperatively and when only radiation therapy was used for treating the total target. This technique gives negligible variations in the absorbed radiation dose in the primary target, but in the secondary target the variations are too high ($\pm 27\%$). A technique with two opposing fields has been used on a few occasions, which gave a satisfactory dose distribution in the target (the variation was 5-10%), and low radiation doses outside the target. This ought to be the most suitable technique now available for treating the inguinal and pelvic lymph node stations postoperatively or when only irradiation is to be used.

The radiotherapeutic techniques used have not only had variations of photon energies, but have also had differing patterns of fractionation. This makes it difficult to evaluate and compare their effects on the tumours. The desirable tumour dose for the future ought to be near the CRE-value for normal connective tissue tolerance in both postoperative irradiation of the lymph node stations and when only radiation therapy is to be used for treating them.

Even with an aggressive primary treatment, recurrences and regional metastases occur in 20-30 % of patients with vulvar squamous cell carcinoma. The treatment of local recurrences in the vulva-vagina-perineum and of regional metastases in the groins is preferably surgical, possibly combined with pre- or postoperative irradiation and chemotherapy. In cases with regional metastases, the prognosis is poor. Patients with primarily advanced "not operable disease", as well as patients with local and regional treatment failures, which appear within six months after termination of primary

treatment, represent a difficult problem. The treatment of choice for these patients is radiotherapy and/or chemotherapy; curative treatment is seldom achieved. Even treatment of short duration, normally gives good palliation, however.

Chemotherapy has not been used in primary treatment with curative intentions. Further investigations with the histological scoring-system may result in possibilities to select a group of biologically aggressive tumours where some form of chemotherapy in combination with surgery and radiotherapy can be recommended as primary treatment.

Reports during recent years, evaluating the effect of chemotherapy in the treatment of malignant melanomas are not impressive (Jönsson 1980, Veronesi 1982, Voigt 1982). If better medical treatment of this disease is discovered, the patients with tumours classified as Clark V or with regional metastases should primarily receive a combination of surgery, irradiation and medical treatment.

CONCLUDING REMARKS

The overall most important prognostic factors for patients with invasive vulvar malignancies are the presence of lymphatic metastases at the time of surgery, and the surgical radicality of the primary surgery.

Treatment recommendations

Squamous cell carcinoma.

1. T₁-tumours with microinvasive growth and without vessel invasion; unilateral tumours: Hemivulvectomy.

Midline tumours: Total vulvectomy.

2. T₁-T₂-tumours with invasive growth and/or vessel invasion; unilateral tumours: Hemivulvectomy combined with preoperative radiotherapy to the groin regions and ipsilateral groin lymphadenectomy.

Midline tumours: Total vulvectomy combined with preoperative radiotherapy to the groin regions and bilateral groin lymphadenectomy.

3. T₃-T₄-tumours: Total vulvectomy combined with preoperative radiotherapy to the groin regions and bilateral groin lymphadenectomy.

A consequent histopathological examination of excised lymph nodes should be done peroperatively in cases where only ipsilateral groin lymphadenectomy is planned. Contralateral groin lymphadenectomy should be done when metastases are found in the excised nodes.

Patients who preoperatively are suspected of having metastases in the lymph nodes, or in whom such metastases are manifest (from histopathological analysis of fine needle puncture) should be treated with preoperative irradiation of the groin and pelvic lymph nodes and with groin lymphadenectomy. Postoperative radiation therapy can also be used, when it is indicated by the findings at surgery. These patients should receive total vulvectomy, irregardless of their T-stages.

Patients with metastases in the lymph nodes demonstrated by histopathologic examination should receive postoperative irradiation of the groin and pelvic lymph nodes.

Malignant melanoma.

All stages: Total vulvectomy combined with preoperative radiotherapy to the groin regions and groin lymphadenectomy. In cases with metastatic groin lymph nodes, also postoperative radiotherapy to the groin and pelvic lymph nodes is advisable.

Basal cell carcinoma.

Local radical extirpation of primary tumour.

ACKNOWLEDGEMENTS

I want to express my sincere thanks to all those who have helped me during this study, and especially to acknowledge:

John-Erik Johnsson, my tutor, for teaching me how to execute science, invaluable positive guidance together with constructive criticism and warm friendship.

Claes Tropé, my tutor, for valuable support, constructive criticism and warm friendship.

Per Alm for the histopathological review and his valuable criticism.

Brita Jönsson, who has been responsible for keeping our time schedule, for accurate typing and lay-out work.

Eva Henriksson for professional help with the figures and lay-out work.

Gertrud Andersson for excellent secretarial work.

Claes Westrup who performed the data-programming.

Jonas Ranstam who helped to carry out the statistical analysis.

Inger-Lena Lamm for technical support and help with radiophysical details.

Ulla-Brita Nordberg for help with radiophysical details.

Birgit Simonsen for secretarial work and help with the English language.

Kenneth Muir for help with the linguistic revision.

Dick Killander for support and interest in the study and valuable criticism.

This work was supported by grants from the John and Augusta Perssons's Foundation for Medical Scientific Research, from the Medical Faculty, University of Lund, and from the Cancer Research Funds of the University Hospital, Lund.

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Annales Chirurgiae et Gynaecologiae (Submitted for publication)

INVASIVE SQUAMOUS CELL CARCINOMA IN THE VULVAR REGION

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SUMMARY

Clinical data on 266 patients with squamous cell carcinoma of the vulva seen between 1960 and 1979 are reported. Two-hundred-eleven of these patients were eligible for 5-year evaluation. The crude survival for these patients was 59 %, and the 5-year crude survival for 195 patients treated with curative intention was 64 %.

Two-hundred-forty-four patients were treated with radical vulvectomy and in 122 patients lymphadenectomy was also performed. Fifty per cent of the patients treated with lymphadenectomy had lymph node metastases at the time of surgery. In 88 % radiotherapy was included in the treatment of the regional lymph node regions.

Treatment failures occurred in 25 % of the patients.

Prognosis was discussed in relation to the tumour size, the tumour site, and the histologic differentiation. The presence of lymphatic involvement and the surgical radicality appeared to be the most significant prognostic factor.

INTRODUCTION

Malignant tumour in the vulvar region represents 5 % of gynecological malignancies and is only the fourth most common gynecological malignant disease after carcinoma of the ovary, the uterine body and the uterine cervix.

In approximately 90 % of malignancies in the vulvar region, the histology is squamous cell carcinoma. 5-8 % are malignant melanomas and 2-3 % are basal cell carcinomas.

Some recent reports show a considerable increase in the incidence of vulvar squamous cell carcinoma during the last 25 years. A Danish report (3), e.g., shows a ten fold increase in the number of cases of invasive vulvar carcinoma recorded from 1950 to 1975 in Denmark. There has not been any significant increase in Sweden during the last 25 years (18, 23).

This increased incidence, also reported from centres in other countries, has resulted in renewed interest in the study of the etiology of vulvar carcinoma. Certain epidemiological correlations have been pointed out. A high frequency of chronic vulvar diseases (30-70 %) has been reported as preceding invasive

carcinoma of the vulva. There is, moreover, an overrepresentation of obesity and diabetes mellitus. An increase in the incidence of premalignant and malignant changes of the cervix have been reported in patients with carcinoma of the vulva. Being associated with cervical carcinoma, herpes virus has been suspected to be a possible etiological factor in this tumour (2, 19, 32).

The treatment results reported for invasive carcinoma of the vulva prior to 1940 were highly unsatisfactory. Surgical treatment limited to local extirpation of the vulvar tumours or radiotherapy of the primary lesion were the commonly applied methods of treatment. The regional lymph nodes were treated only in a very few cases. Five-year survival in more than 10-20 % of the patients was rare (33).

A better understanding of the nature, the growth and the lymph drainage of the vulvar carcinoma resulted in S. Way's and F.J. Taussig's principles on the surgical treatment of carcinoma of the vulva. These still form the basis of the treatment given at most centres today.

For the past 40 years, the most widely accepted therapy for carcinoma of the vulva has been radical vulvectomy with inguinal and pelvic lymphadenectomy. S. Way (34) established that the survival was directly related to a wide and deep removal of the vulva coupled with an aggressive attack on the regional lymph nodes.

The technique has, however, been improved through the years since 1940. In certain centres, surgical aggressiveness has been increased and pelvic exenteration in some form is included in 10-20 % of the cases treated.

This aggressive surgical treatment can, however, increase the 5-year survival rate marginally, only at the cost of high complication rates and a significant surgical mortality.

In other centres, a more individualized treatment, often including less aggressive surgery has been applied. Open wound-technique using warm knife or laser beam, and sometimes in combination with radiotherapy has been practiced due to the advanced age of this patient group and the high incidence of complications associated with aggressive surgery (3, 6, 17, 28).

The purpose of this report is to account for the treatment results obtained

in 266 consecutive cases of squamous cell carcinoma of the vulva treated in accordance with the principles described below during the 20-year period between 1960 and 1979, in order to evaluate the prognostic significance of the size and site of tumour, histologic differentiation and lymph node involvement.

MATERIAL AND METHODS

During the period 1960-1979, a total of 317 patients with malignant tumours of the vulva have been admitted for treatment at the Gynecologic Section, Department of Oncology, University Hospital of Lund. The histological distribution is shown in Table I. In 266 patients, the histological diagnosis was squamous cell carcinoma and these patients form the basis of this report. The mean age was 68 years (range 19-96), and the median age was 70.

Table I. Histopathological findings in 317 patients with malignant vulvar tumours.

Histology	No. of patients
Squamous cell carcinoma	266
well differentiated	183
moderately differentiated	62
poorly differentiated	21
Malignant melanoma	25
Basal cell carcinoma	14
Morbus Paget	4
Anaplastic carcinoma	2
Adenocarcinoma	2
Adenosquamous carcinoma	1
Lymphoma	1
Rhabdomyosarcoma	1
Leiomyosarcoma	1
Total	317

Twenty-five per cent of the patients had previously received treatment for other vulvar diseases (e.g. Lichen sclerosis and hyperplastic dystrophy) prior to the diagnosis of squamous cell carcinoma of the vulva.

This figure is probably too low in comparison with other reports (32) but this can probably be explained by inadequate patient records.

Table II. Previous malignant diseases.

	No. of patients
Cancer mammae	8
Cancer cutis	8
Cancer colli uteri	3
Cancer corporis uteri	2
Malignant melanoma	1
Cancer ventriculi	1
Cancer renis	1
Total	24

Table III. First symptoms as reported by the patients at the first consultation.

	No. of patients
Itching	121
Bleeding	24
Mass	84
Groin nodes	5
Itching and bleeding	5
Itching and mass	9
"No symptoms/don't remember"	18

In this patient material, 8.5 % have previously had other malignancies (Table II). Information from the patients regarding primary symptoms and signs is listed in Table III. Fourteen patients indicated several different symptoms as occurring simultaneously and 18 patients could not recall their primary symptoms.

Table IV. Localization of the tumour.

	No. of patients
Clitoris region	78
Urethra	7
Right labium majus/minus	61
Left labium majus/minus	70
Vulva + perineum-anus	16
Exophytic growth, right and left sides	21
Not possible to evaluate	13
Total	266

Table V. The time lapse between the first symptom and the first consultation.

"Delay"	No. of patients
2 - 6 months	107
>6 - 12 months	56
>1 - 5 years	46
>5 years	9

Table IV shows the tumour sites. The most common sites were the labium majus and the labium minus, with the same incidence for the right and left sides. As reported previously (3, 13, 18, 36) a long delay from the occurrence of the primary symptom until the initiation of treatment has been recorded in many cases (Table V). The most significant delay was between the time of the

primary symptom and the first consultation, but also a significant doctor's delay was found.

Staging: The patients were staged according to the UICC (TNM) and the FIGO classifications (8) (Tables VI, VII and VIII). The histological distribution is shown in Table I. The distribution of tumour size (T_1 - T_4) is shown in Table IX.

Table VI. TNM system according to UICC.

T	Primary tumour
T_1	Tumour confined to vulva - 2 cm or less in diameter
T_2	Tumour confined to vulva - more than 2 cm in diameter
T_3	Tumour of any size with adjacent spread to the urethra and/or vagina, and/or perineum, and/or to the anus
T_4	Tumour of any size infiltrating to bladder mucosa and/or the rectal mucosa or both, including the upper part of the urethral mucosa and/or fixed to the bone
N	Regional lymph nodes
N_0	No nodes palpable
N_1	Nodes palpable in either groin not enlarged mobile (not clinically suspicious of neoplasm)
N_2	Nodes palpable in either one or both groins enlarged, firm and mobile (clinically suspicious of neoplasm)
N_3	Fixed or ulcerated nodes
M	Distant metastases
M_0	No clinical metastases
M_1	(a) palpable deep pelvic nodes
M_1	(b) other distant metastases

Table VII. FIGO classification according to the TNM system

Stage I	T ₁	N ₀	M ₀
	T ₁	N ₁	M ₀
Stage II	T ₂	N ₀	M ₀
	T ₂	N ₁	M ₀
Stage III	T ₃	N ₀	M ₀
	T ₃	N ₁	M ₀
	T ₃	N ₂	M ₀
	T ₁	N ₂	M ₀
	T ₂	N ₂	M ₀
Stage IV	T ₁	N ₃	M ₀
	T ₂	N ₃	M ₀
	T ₃	N ₃	M ₀
	T ₄	N ₃	M ₀
	T ₄	N ₀	M ₀
	T ₄	N ₁	M ₀
	T ₄	N ₂	M ₀
and all others with M ₁ (a) and M ₁ (b)			

Table VIII. The classification according to FIGO.

FIGO Stage	No. of patients
I	86
II	67
III	76
IV	37
Total	266

Table IX. The distribution of patients in relation to the tumour size.
TNM system (UICC).

Size T	No. of patients
T ₁	102
T ₂	99
T ₃	55
T ₄	10
Total	266

Treatment: The same treatment principles have been used during the last 20-year period. The patients have been treated with combined surgery and radiation therapy. Chemotherapy has only been used as a palliative procedure or in combination with surgery and radiotherapy in cases with treatment failures.

Surgery: Radical vulvectomy using warm knife- and open wound-technique was performed in 244 patients as the first step in the two-phase surgical approach. Using warm knife-technique, the vulva was removed with its underlying subcutaneous tissues and muscles. The median limit of the dissection was the hymenal ring, leaving the urethra intact. The lateral limit was the labio-crural fold, crossing the perineum above the anus caudally and mons veneris cranially, with the intended minimal free margin to the tumour of 2 cm. Individualization of the resection line, however, was sometimes necessary in the patient material studied here, because of the localization and extent of the tumour. The excision was done to the deep fascia. Excision of parts of the urogenital diaphragma and the distal part of the urethra, as well as dissection of paravaginal and ischorectal spaces, were sometimes done as well. After removal of the operation specimen, the wound surfaces were diathermically coagulated, partly to stop the bleeding and partly to destroy the tumour cells eventually left in the operation area. The wound was left open for secondary healing.

A Dextran solution with penicillin and boracic vaseline were applied alternatively during the initial ten days for the treatment of the local wound, after which time only boracic vaseline was used. An indwelling catheter was

installed for 3-5 days. The operation technique is described in more detail in an earlier report (29).

Lymphadenectomy was performed six weeks later if the general condition of the patient so permitted. The lymphadenectomy was generally formed as bilateral inguinal lymphadenectomy. Pelvic lymphadenectomy was performed in cases where a clinical preoperative examination revealed metastasis in the inguinal lymph node stations. The surgical technique for inguinal lymphadenectomy includes dissection of the inguinal nodes, stripping of the femoral vessels and deep fascia from muscles. With pelvic lymphadenectomy we do not use to split the inguinal ligament, but we are sweeping the perineum medially to expose the external iliac vessels up to the bifurcation of the common iliac vessels, in order to allow removal of the interiliac lymph nodes as well. These surgical principles have changed only moderately during the 20-year period of the study. Only few cases necessitated a deviation from the two-step procedure and if so, only in relatively advanced cases, where the inguinal lymph nodes were initially found with clinically manifest metastasis. The distribution of curative surgical treatment varying from partial vulvectomy to radical vulvectomy plus bilateral inguinal and pelvic lymphadenectomy is shown in Table X. Inguinal lymphadenectomy is in principle always carried out bilaterally, except in cases where during operation of the primary side, it was determined that radical surgery could not be performed, and surgical treatment on the other side was then abandoned.

Three patients have received palliative surgery only, consisting of partial vulvectomy. Nineteen patients with advanced carcinoma, advanced age or with a negative attitude towards surgical treatment have received palliative treatment with irradiation and/or chemotherapy, but without any kind of surgery. Sixteen of these patients had been staged as FIGO III or IV.

Table X. Primary surgical treatment technique.

Surgery	Stage I	Stage II	Stage III	Stage IV
Vulvectomy + groin dissection	34	25	30	7
Vulvectomy + groin and pelvic dissection	1	7	11	7
Partial vulvectomy	6	3	-	-
Radical vulvectomy	43	29	30	11

Radiotherapy: External irradiation has been given to the local tumours in advanced cases in order to make them operable. Surgery, if possible, was performed about six weeks after conclusion of this treatment. Single-field technique was used and a peak absorbed dose of 3 Gy per fraction, three fractions a week, to a total of 24-51 Gy. Depending on the calculated depth of the tumour infiltration, the tumour size and site photons from a ^{137}Cs -unit, a ^{60}Co -unit or 15-35 MeV electrons were used.

Preoperative irradiation to the groin region has been given in connection with the vulvar surgery, six weeks prior to lymphadenectomy. From 1960-1962, a decacurie-unit was used for this preoperative treatment. From 1963-1979, a ^{137}Cs -unit was used with single-field technique, a field size of 8 x 13 cm and SSD 20 cm. The peak absorbed dose was 7 Gy per fraction. Three fractions a week up to a total of 21 Gy was given. The deepest part of the target, representing the inguinal nodes, was assumed to be located 3 cm below the skin surface. This will give a target absorbed dose (specification point on the central axis at the centre of the target area) of 17.6 Gy.

When metastatic nodes were determined microscopically in the surgical specimens, the inguinal region and the pelvic nodes on the sides in question were given postoperative external irradiation as a rule using a ^{60}Co -unit with single-field technique, SSD 80 cm and a field size of about 150 cm². The peak absorbed dose was 3 Gy per fraction, five fractions a week up to a total peak absorbed dose of about 24 Gy to about 33 Gy, respectively, depending on the findings in the surgical specimens (metastatic growth in the nodes only or metastatic growth outside the nodes). The deepest part of the target, representing the operation area and the external and interiliac lymph nodes were assumed to be located 10 cm from the skin surface. The target absorbed dose (specification point on the central axis at the centre of the target area) was 9.6 Gy to 33.6 Gy, respectively. The radiotherapeutic technique has been improved and the standard target volumes have been changed during the 20-year period. The irradiation technique is described in detail in an earlier report (30). Patients not operated with lymphadenectomy have been given radiotherapy to the groins with a total absorbed target dose from 17.6 to 42.8 Gy.

In 12 % of the patients, this irradiation was not performed because of advanced patient age and very early carcinoma.

Most patients were followed at the Department for a minimum of 10 years after

initial treatment. Only about 5 % were checked in their local hospital. No patient was lost to follow-up, the observation time was 2 to 20 years.

RESULTS

Postoperative complications: No per- or postoperative mortality was observed in this material. The mean hospitalization time for vulvectomies as well as for lymphadenectomies has been 16 days.

Stricture at the introitus, prolapsus and wound infection are common complications in connection with vulvar surgery. The frequency of these complications are, however, difficult to evaluate in a retrospective study. When using warm knife-technique without primary closing for vulvectomies, stricture at the introitus vaginae is a not uncommon complication (9, 16). In this material, however, surgical correction was considered necessary in only 12 patients. Prolapsus is more rare, and in this material corrective surgery has been performed in only five patients. Uncomplicated, primary wound infections are often reported. These are easily cured by administration of local and/or general antibiotic therapy and do not result in impairment of the wound healing. In only nine cases has the infection necessitated antibiotic treatment of longer duration and surgical wound revision was necessary. Two cases of sepsis have been successfully treated. One case of osteitis in the pubic bone required six weeks antibiotic therapy.

A varying degree of edema in the lower limbs is the most common complication of lymphadenectomy. Edema occurring 6-12 months after lymphadenectomy is frequently reported. Twenty-one patients with leg edema which has necessitated e.g. diuretical treatment or orthopedic stocking were registered. Eight cases of thrombosis in the lower extremities were observed postoperatively, of which three were complicated by pulmonary embolism.

The histopathological examination of the surgical specimens has indicated radicality (≥ 1 cm free resection margin) in 70 % of the cases, doubtful radicality (< 1 cm free resection margin) in 16 % and non-radical intervention (tumour growth in the resection border) in 18 %.

The percentage of patients who underwent surgery defined as non-radical increases with tumour size (T_1 - T_4) and an equal increase of the recurrence rate has been recorded (31).

Lymph node metastases: The occurrence of metastases in relation to tumour size is accounted for in Table XI. The metastatic incidence increases T_1 to T_4 . Of a total of 122 patients who underwent lymphadenectomy, 62 (51 %) had metastases in the lymph nodes. Among the 26 patients who underwent dissection of the pelvic nodes 12 (46 %) had metastases in the pelvic lymph nodes. Involved inguinal nodes on the same side were found in these 12 patients.

Table XI. Frequency of metastases, in relation to the tumour size, using the TNM system.

"T"	No. of patients	Groin gland	Pelvic gland	%
T_1	45	12	4	31
T_2	55	35	4	70
T_3	20	13	4	85
T_4	2	2	—	100
Total	122	62	12	

Treatment failures: Of the group who underwent curative treatment, 244 patients, treatment failures (local recurrence, regional or distant metastasis) appeared within six months after primary treatment (in 19 cases). Treatment failure appearing more than six months after primary treatment occurred as local recurrences in 29 patients, and regional or distant metastases in 15 patients.

Twenty-five per cent of the patients developed treatment failures from 0-16 years after primary treatment. Ninety per cent of the failures were diagnosed within two years after primary treatment. The recurrence incidence and timing increases with tumour size. As reported by others, extremely few recurrences were recorded with tumour size of less than one cm in diameter. Early local recurrences have a poor prognosis and occur often in patients not receiving radical surgery. Regional metastases always have a poor prognosis (7, 31).

Surgery, chemotherapy, and irradiation have been used in treatment failures. A combination of treatment modalities is commonly used. Relapse has occurred in several patients. Only 20 % of the patients treated for recurrences and metastases are alive five years after their first relapse (7, 31).

Table XII. Five-year crude survival in relation to the stages according to the FIGO classification.

Survival	No. of patients	Dead in cancer	Dead in ICD	5-year crude survival
Stage I	67	6	7	81 %
Stage II	51	13	5	65 %
Stage III	64	25	7	48 %
Stage IV	29	19	5	21 %
All stages	211	63	24	59 %

Survival rate, %

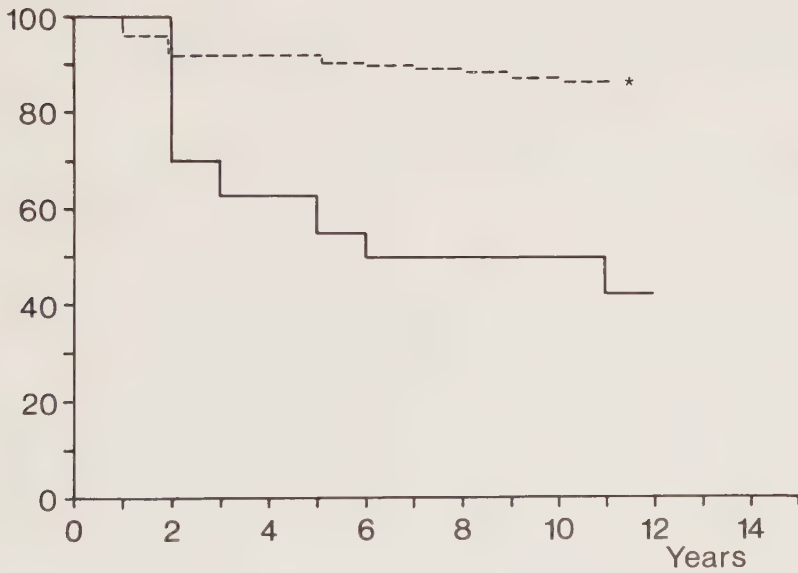


Fig 1a. Survival rate for the total group (n=266). *General population.

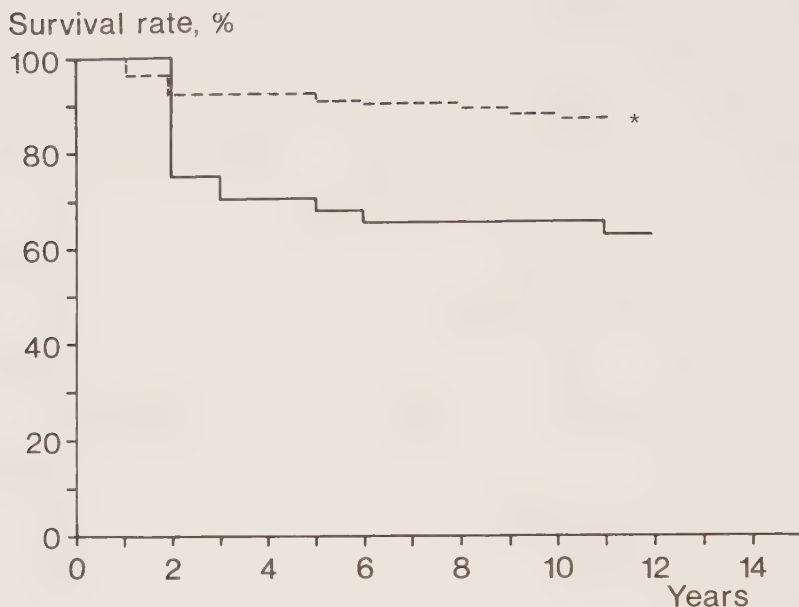


Fig 1b. Survival rate corrected for mortality due to intercurrent disease.

*General population.

Five-year crude survival rate could be calculated in 211 out of 266 patients with squamous cell carcinoma. Table XII shows the crude survival in the different stages.

Five-year crude survival was 59 %, for those 195 patients who underwent surgery, with curative intention, the corresponding figure was 64 %. Survival using life-table technique (26) for the total group (266) is shown in Fig 1a. Survival rate corrected for mortality due to intercurrent disease is shown in Fig 1b. Survival in relation to the size of tumour, stage, and primary tumour site is shown in Figs 2, 3 and 4.

Survival correlated to histologic differentiation is shown in Fig 5. Moderately and poorly differentiated tumours had non-significantly poorer prognoses than the well differentiated ones. No differences in local and regional treatment failures were observed between well, moderate and poor differentiation. This agrees with most reports in the literature (13, 20, 24), although some few studies have asserted a significantly poorer prognosis for poorly differentiated vulvar tumours (35).

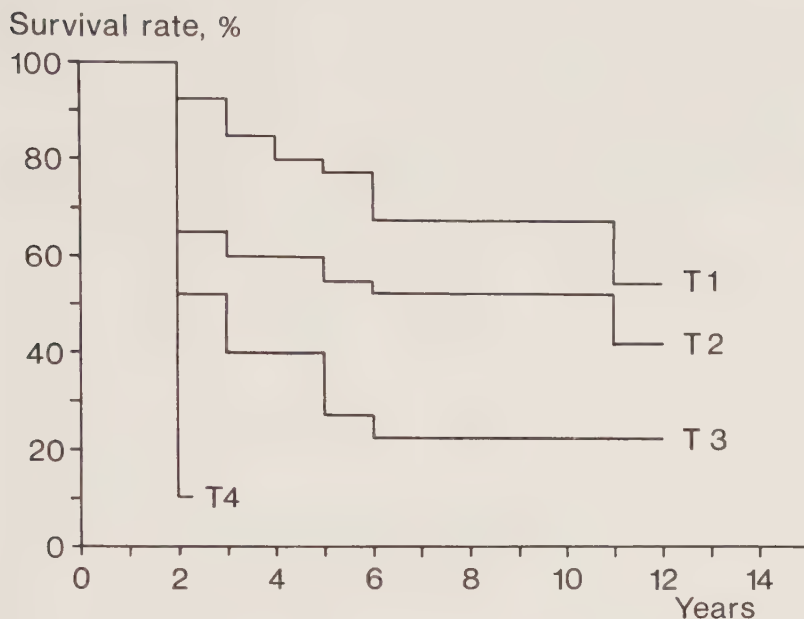


Fig 2. Survival rates correlated to tumour size, TNM system (UICC),
 T_1 (n=102), T_2 (n=99), T_3 (n=55), T_4 (n=10).

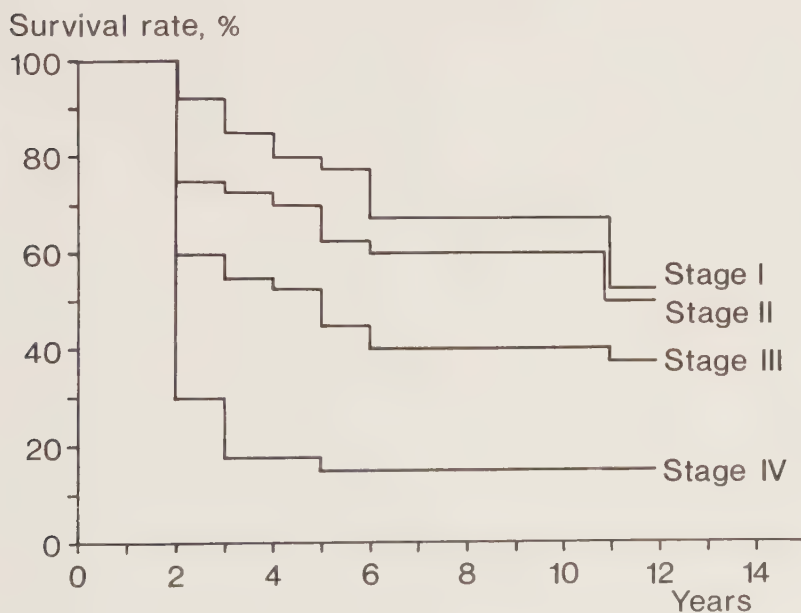


Fig 3. Survival rates correlated to tumour stage (FIGO). Stage I (n=86),
 Stage II (n=67), Stage III (n=76), stage IV (n=37).

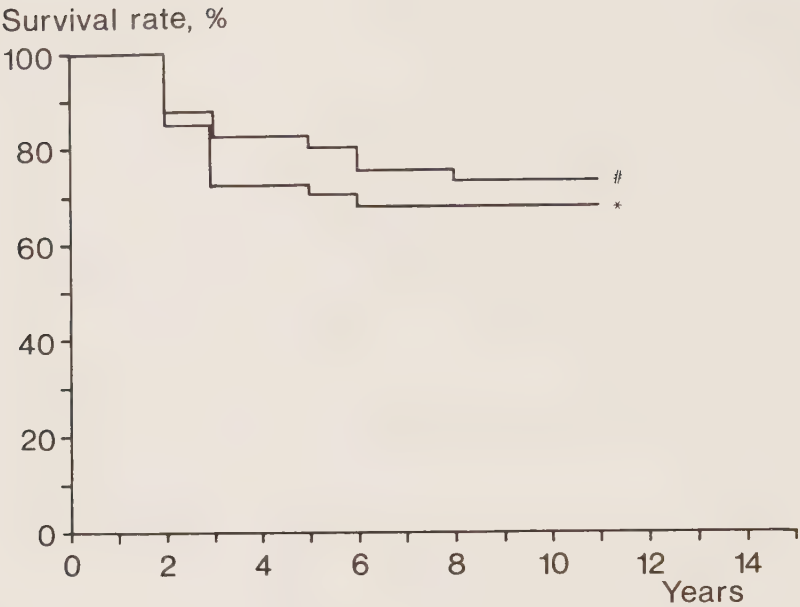


Fig 4. Survival rates for T₁-T₂ tumours located in the clitoris region (n=68)* and at the labia pudendi (n=120)#.

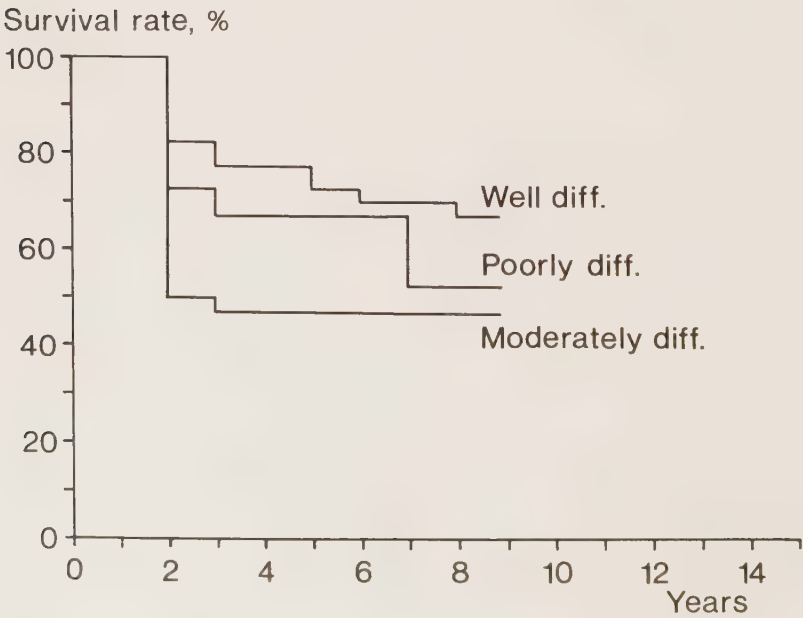


Fig 5. Survival rates correlated to histologic differentiation. Well diff (n=183), moderately diff (n=62), poorly diff (n=21).

DISCUSSION

A comparison between the survival rates presented in different reports is difficult, due to variation in the classification and selection of the patient material. The reporting of "corrected" survival rates by eliminating deaths due to intercurrent disease is not uncommon but rarely disclose how the figures were arrived at. In a group of patients with a median age of 70 years, death due to intercurrent disease is of significance, but at the same time, it is well documented that many reports indicate an increase in the intercurrent death rate from the Stage I group to Stage IV group.

It is consequently our intention to report the 5-year crude survival rate for all patients with at least five years observation time and to complete a life-table analysis of the total material. In comparing the survival rate for this series of patients with those reported by others, the following factors must be taken into consideration. Our definition of "crude 5-year survival" means that a patient is not excluded from the material if death occurred from intercurrent disease or due to accident. Most other reports only deal with series of surgically treated patients. Morely, 1976 (21) analysed a series of 299 patients in whom the 5-year absolute crude survival rate was 66.8 %. Green, 1978 (12) reported a 5-year survival for 107 patients as 64 %. Franklin and Rutledge, 1971 (10) reported on a series of 164 patients, and the absolute 5-year survival rate for 81 patients was 55.7 %. Japaze et al, 1976 (15) reported a 5-year survival rate of 50 % for 121 cases. Benedet et al, 1979 (4) reported a series of 264 patients treated between the years 1938-1976, in whom the 5-year survival rate for all stages was 55 %.

Deaths due to carcinoma of the vulva mainly occur within the first 2.5 years after initial treatment (Fig 1b). Deaths due to intercurrent disease are of decisive importance.

An increasingly poor prognosis is recorded from Stage I to Stage IV, and a similar increasingly poor prognosis is seen with increasing tumour size (from T₁ -T₄, Figs 2 and 3). The correlation between metastatic incidence and tumour size is shown in Table XI.

The different local recurrence rate in various reports are probably due to variation in selections of the patient materials, and the operation technique used and the length of the observation period. However, local recurrence rate of 21 % in this material for surgically treated patients with an observation time of at least five years did not significantly differ from

other reports (3, 13, 27). Early occurring recurrences (<6 months) indicate a very poor prognosis: no survival was registered after five years. A great part of patients in this group was not initially treated with radical surgery. Local recurrences occurring later on are often successfully treated with secondary surgery and with a rather good prognosis (31). Survival correlated to recurrence is shown in Figs 6, 7 and 8.

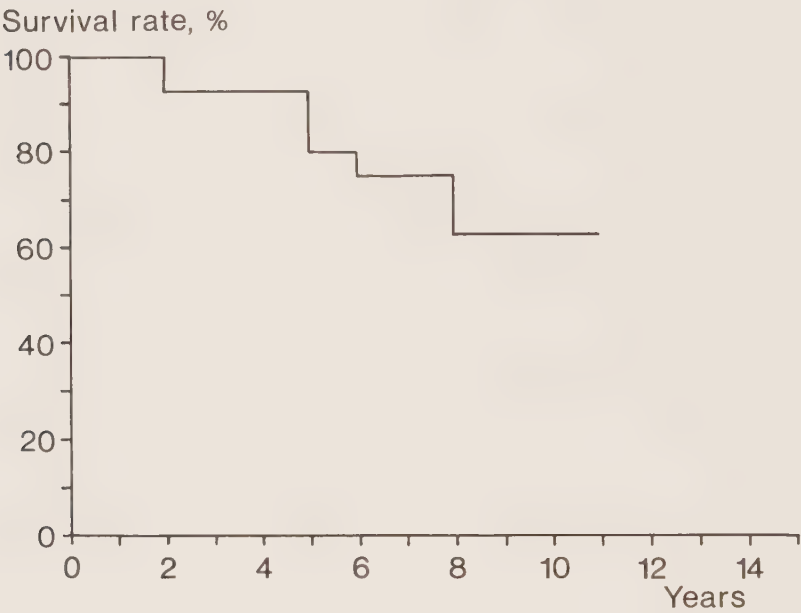


Fig 6. Survival rate for patients with only local recurrence appeared more than six months after conclusion of primary treatment (n=24).

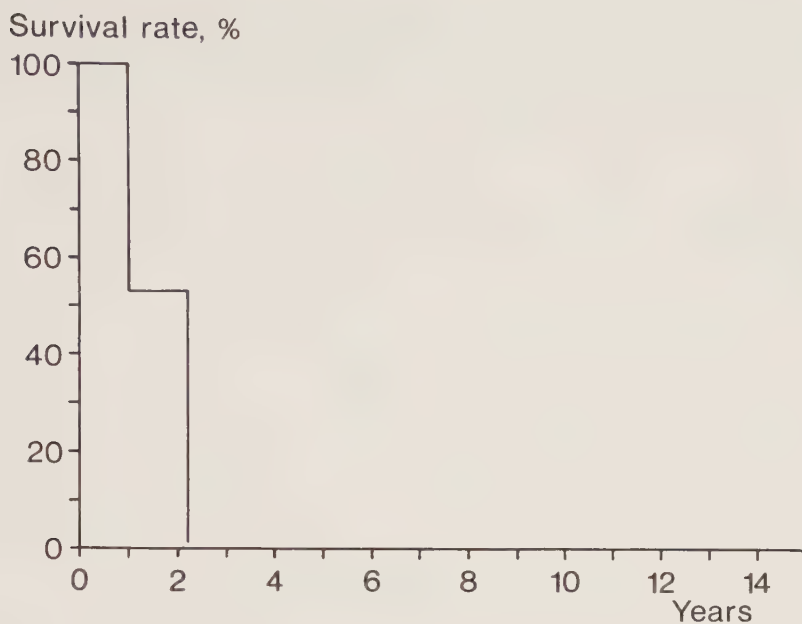


Fig 7. Survival rate for patients with tumour progression during the primary treatment or within the following six months (n=19).

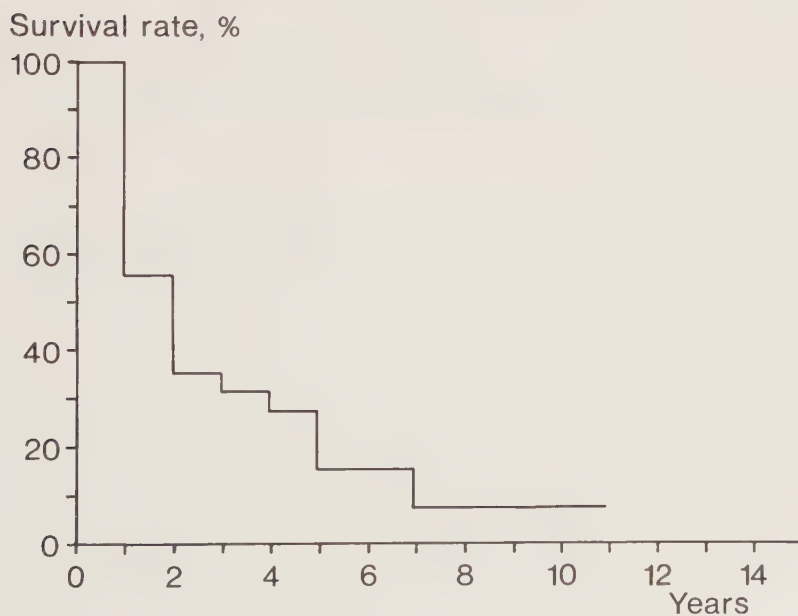


Fig 8. Survival rate for patients with regional metastases appeared more than six months after conclusion of primary treatment (n=17).

There are conflicting opinions whether tumours in the clitoris area are more aggressive than in other tumour locations and having a poorer prognosis (3, 11, 20, 25, 27). The present series has shown only slightly poorer prognosis for tumours near the clitoris (Fig 4).

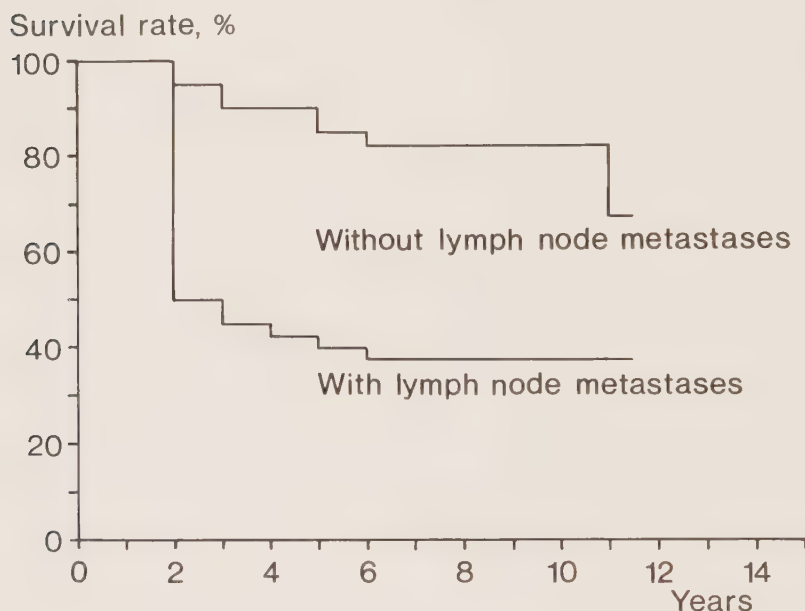


Fig 9. Survival rates correlated to involvement of lymph nodes at primary surgery. With metastases (n=62), without metastases (n=60).

Metastatic lymph nodes (Fig 9) are associated with poor prognosis. The 5-year survival rates for patients who underwent lymphadenectomy (122), were 40 % for patients with metastatic nodes and 82 % for patients with non-metastatic nodes.

Lymph node dissection was performed only in 122 cases (46 %). The reason for abstaining from nodal surgery have been advanced age and/or early carcinoma. In the group that underwent surgical treatment of the vulva but only received radiotherapy of the lymph node region, there were 91 cases (34 %), Stages I and II (T_1N_0) (T_2N_0). Most of the lymphadenectomized patients had Stage II to IV tumours. It might be expected to find a rather high metastatic frequency in extirpated lymph nodes, 62 of 122 (51 %) when inguinal lymphadenectomy was performed, and 12 of 26 (46 %) when pelvic lymphadenectomy was performed. The fact that pelvic lymphadenectomy is only performed in cases where a

clinical peroperative examination confirms inguinal lymph node metastasization is another reason for finding a high frequency of metastases in extirpated pelvic nodes and the presence of pelvic metastases are seldom seen without inguinal lymph node metastases (3, 13, 21).

Pelvic lymphadenectomy is regarded by some as general routine surgery, whereas others regard it as necessary only with clitoris localization and with infiltration of the vagina (22, 28, 34, 36). Several authors, however, question the indication for this surgical approach, which tends to increase the surgical trauma, increases the already extensive operation time and also the surgical mortality rate (3, 13).

As it would appear from most reports (3, 13, 21, 22), the 5-year survival rate is only marginally improved by pelvic lymphadenectomy. In several investigations, no 5-year survival rates are recorded for patients with metastatic pelvic nodes. In this material, three of 12 patients with metastatic pelvic nodes have survived five years. The role of given radiotherapy to the regional lymph node station is difficult to evaluate and the material is very small. The disease is likely to be disseminated in cases with pelvic lymph node metastases and surgery will only seldom be advisable.

The recommended treatment during recent decades has been total vulvectomy and bilateral lymphadenectomy. Bilateral lymphadenectomy is recommended because some authors (36) have recorded unilateral tumours, with only contralateral metastases in the inguinal and/or pelvic nodes, in 5 % of the patients.

In this material the metastases in patients with unilateral tumour and microscopically confirmed metastatic nodes have all been located to ipsilateral nodes, or in some cases, in both contra- and ipsilateral lymph nodes, but in no cases only in the contralateral side. Midline tumours (clitoris, urethra, perineum) have shown equal incidence of nodal involvement in the right and left sides, which seems to be true for pelvic nodal metastases as well. No correlation between increase frequency of metastases to the pelvic nodes have been observed in tumours of the clitoral region.

CONCLUSIONS

With combination therapy of surgery and irradiation, and the two-step surgical procedure, we have had a low complication rate and a short hospi-

talization. These factors must be interpreted as very important, in particular since our 5-year survival rate, compared with other reports is not low, and the median age of our patients was very high.

The prognosis is increasing for Stage I to Stage IV and similar figures are seen for tumour size T_1 to T_4 , Figs 3 and 4 . The tumour site and the histologic differentiation have nearly non prognostic significance.

The result of the recurrence treatment is generally unsatisfactory. Regional recurrences are difficult to treat and have a poor prognosis.

The overall most important prognostic factors are the presence of lymphatic metastases at the time of surgery, and the surgical radicality with the primary surgery.

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Acta Radiologica (Accepted for publication)

STAGE I SQUAMOUS CELL CARCINOMA OF THE VULVA

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SUMMARY

Eighty-six patients with invasive squamous cell carcinoma of the vulva stage I were followed for 2-20 years after surgical treatment varying from local excision to radical vulvectomy with inguinal lymph node dissection. In 87 % of the patients external irradiation was applied to the inguinal regions in connection with the vulvar surgery. Seven of 35 patients who underwent additional lymphadenectomy had metastases to the inguinal lymph nodes. Five-year crude survival rate for the whole series was 81 %.

The prognosis was discussed in relation to the radicality of the surgical intervention, the degree of tumour differentiation, the morphologic properties of tumour cell population and tumour host relationship. It seemed that the most important prognostic factor was the radicality of the surgical intervention.

In efforts to reduce patient morbidity in radical surgery but still achieving comparable survival date, an operative approach less than radical vulvectomy, inguinal dissections, and/or pelvic lymphadenectomy is proposed for selected patients.

INTRODUCTION

Stage I of vulvar carcinoma is defined by the FIGO-classification as including tumours up to 2 cm in their largest diameter, and without palpable lymph nodes in the groin, or as having palpable lymph nodes not suspected for metastases as judged from clinical evaluation.

This definition has been criticized asserting that the depth of infiltration ought to be specified, and that the limit of tumour size, i.e. 2 cm in diameter, has not proven to be satisfactory for prognostic evaluation (Rutledge et coll 1970, Parker et coll 1975, Friedrich & Di Paolo 1977, Green 1978, Andreasson et coll 1980, Iversen et coll 1981).

Various treatment modalities of stage I vulvar carcinoma (Dean et coll 1974, Wharton et coll 1974, Parker et coll 1975, Friedrich & Di Paolo 1977, Kuschner et coll 1978, Disaia et coll 1979, Magrina et coll 1979, Iversen et coll 1981) have been suggested. A number of authors have attempted to use histological parameters such as depth of tumour growth and occurrence of vascular invasion (Wharton et coll 1974, Parker et coll 1975, Buschema et coll 1980, Buschema et coll 1981, Iversen et coll 1981) in order to get

more individualized and less traumatic therapy than the generally accepted measures to-day for all stages of squamous cell carcinoma of the vulva: vulvectomy and lymphadenectomy, which appear to be too extensive and unnecessarily aggressive for these early tumours.

The aim of the present study has been to present the results of therapy obtained in stage I of vulvar squamous cell carcinomas, and to evaluate the clinical and histological factors which can have bearing on the prognosis, leading to more differentiated forms of treatment.

MATERIAL AND METHODS

A total of 317 patients with malignant tumours of the vulva have been referred to the Gynecologic Section of the Department of Oncology in Lund during the 20-year period 1960-1979. The diagnosis of squamous cell carcinoma was confirmed in 266 of these patients, of whom 86 were classified as being in stage I. These 86 patients constitute the basis of the present study.

The average age was 65 years (ranging from 35-86 years); median age was 66 years. About 25 % of the patients had earlier been treated for vulvar disease, especially for Lichen sclerosus and hyperplastic dystrophy. Nine patients (10 %) had some other malignant disease in their case histories (4 cancer mammae, 2 cancer colli uteri, 2 cancer cutis, 1 cancer coli).

The most common initial symptom noted was itching and/or pain, reported by 42 patients (49 %). Thirty-two patients (37 %) first noted palpable hard-nesses of tissue, or sores, while seven (8 %) initially had bleedings. Five patients could not state the primary symptom.

Delay in seeking medical care after the onset of symptoms varied between two weeks and ten years: 51 (59 %) 0-6 months; 13 (15 %) >6-12 months; 16 (19 %) >1-5 years; 6 (7 %) more than five years.

The tumour was located in the labia majora pudendi or the labia minora pudendi in 47 patients (55 %), in the area around the clitoris in 26 cases (30 %) and in the posterior commissurae in 4 patients (5 %). The exact site of the primary tumour could not be established in 9 cases (10 %).

Surgery had been performed as partial or radical vulvectomy utilizing electroresection with open-wound technique (SIMONSEN et coll 1982). Radical vulvectomy was performed in 78 patients, partial vulvectomy in six cases and local excision only in two patients.

About eight weeks after the radical vulvectomy, groin dissection was performed in 35 out of the 78 patients. In one patient, the groin dissection was supplemented with pelvic lymphadenectomy. In 68 (87 %) of the 78 patients, external irradiation was applied to the inguinal regions in connection with the vulvar surgery.

A ^{137}Cs -unit was used with single-field technique, with a field size of 8×13 cm and SSD = 20 cm. The peak absorbed dose was 7 Gy per fraction, with three fractions a week up to a total of 21 Gy, given before the lymphadenectomy. The deepest part of the target, representing the inguinal nodes, was assumed to be located 3 cm below the skin surface. Obtaining a target absorbed dose (specification point on the central axis at the centre of the target area) of about 17.6 Gy. Patients not operated with groin lymphadenectomy have with increasing frequency been given additional radiotherapy during recent years. Of these 43 patients 21 were given a target dose of 17.6 Gy and 15 were given a target dose from 21 up to 38 Gy. Seven patients were not given radiotherapy at all.

When metastatic nodes were detected microscopically in the surgical specimens, the inguinal region and the pelvic nodes on the respective side were given additional external irradiation using a ^{60}Co -unit with single-field technique and SSD = 80 cm, with a field size of about 150 cm^2 . The peak absorbed dose was 3 Gy per fraction, and five fractions a week were given up to a total peak absorbed dose of 24 or 33 Gy, depending on the findings in the surgical specimens (metastatic growing only in the nodes, or metastatic growing outside the nodes). The deepest part of the target, representing the operation area, the external and the interiliac lymph nodes, was assumed to be located 10 cm below the skin surface and resulting in a target absorbed dose (specification point on the central axis at the centre of the target area) of about 19.2 or 26.4 Gy.

All surgical tissue specimens were fixed in formol and further embedded in paraffin. The specimens were re-examined and classified by the same pathologist.

The degree of differentiation (well, moderately or poorly differentiated) was based on the least differentiated elements in the specimens (Ackerman & Del Regato 1947). In 77 patients the future prognoses were estimated from properties of the tumour cell population: structure, differentiation into cell type, nuclear polymorphism, mitosis and the tumour host relationship: mode of invasion, stage of invasion, vascular invasion, (lympho-tic) cellular response, were graded according to a point-score system used for squamous cell carcinoma of the larynx (Jakobsson 1973, Jakobsson et coll 1973), the palate (Eneroth & Moberger 1973), the gingiva (Willén et coll 1975), the uterine cervix (Stendahl et coll 1979) and the vulva (Kabulski & Frankman 1978). Each parameter was given 1 to 3 points resulting in a total of 8 to 24 points in increasing grade of malignancy. The total point-score values were compared with 5-year crude survival to find out whether the point-score system could be used for prognostic purposes also in stage I vulvar squamous cell carcinomas. In four cases the histological specimens could not be refound and in five cases they were not evaluable.

The surgical intervention was defined as radical if the distance from the tumour to the resection margin as judged from histopathological examination exceeded 1 cm; if it was 1 cm or less, the radicality was considered dubious. Tumour growth in the resection margins meant a non-radical intervention. Treatment failures registered in the perineum, the vulva, the lower half of the vagina or in the urethra were classified as local recurrences. Metastases to groin lymph nodes and/or pelvic wall lymph nodes after completion of treatment were defined as regional metastases. Spreading to organs outside the small pelvis was defined as distant metastases.

Prognosis was defined in terms of five-year survival according to life-table analysis. Multivariate analysis by Cox's proportional hazards model has been used for working out the scoring system.

RESULTS

The prognoses calculated with life-table analysis are shown in Fig 1. In the 67 patients for whom five-year survival could be calculated, six succumbed from the cancer disease and seven patients expired from intercurrent disease, the five-year crude survival was 81 %. Two of the six patients dying from the tumour disease within five years had symptoms more than 6-12 months before the beginning of treatment, and four had had symptoms from 1-5 years prior to therapy. Three of the patients had tumours in the clitoris region and the

other three had tumours in the labia minora pudendi or in the labia majora pudendi.

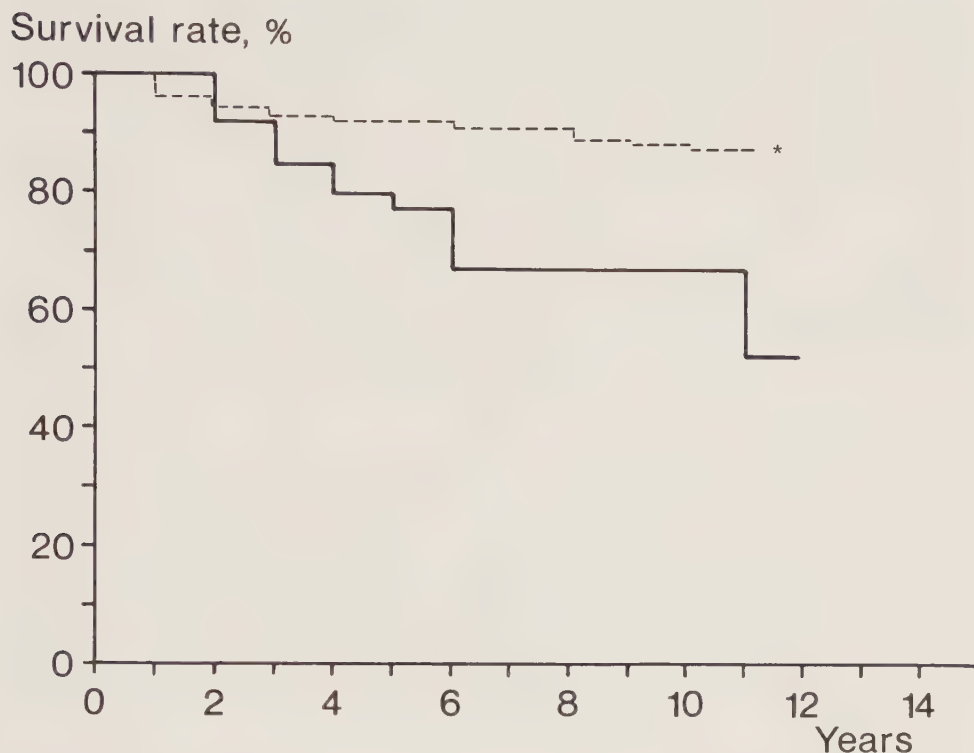


Fig 1. Median survival for stage I 11.0 years (n = 86). *General population.

Of eight patients who died from the cancer disease after periods of observation varying from two to five years, five had undergone radical vulvectomy and received irradiation of the groins. Three had had radical vulvectomy, radiation therapy of the groins and inguinal lymphadenectomy.

In Table I survival rates and the frequency of recurrences and metastases in relation to primary surgery are shown.

Local recurrences were recorded for 18 patients (21 %) and in 8 of these the primary surgical treatment were of doubtful radicality or non-radical. The corresponding figure for the 68 patients without local recurrences was 12. The five of the eight patients who died of cancer was adjudged as non-radical or of doubtful radicality.

Table I. Primary treatment technique and type of treatment failure.

Primary treatment technique	No. of cases	Local recurrences	Regional metastases	Local recurrences and regional metastases	Death in carcinoma ≤ 5 years
Hemivulvectomy	6	1	-	-	-
Vulvectomy	43	6	-	-	-
		-	5	-	4
		-	-	3	1
Vulvectomy and groin dissection with metastases	7	-	-	2	1
Vulvectomy and groin dissection without metastases	28	5	-	-	-
		-	2	-	2
Local excision	2	1	-	-	-

One of the two patients, treated with only local tumour excision, was further treated with radium needles implanted in the area of the incision. Two years later she underwent vulvectomy and bilateral groin dissection because of local tumour recurrence. No metastases were found in the excised lymph nodes. This patient was still alive after an observation period of sixteen years.

Metastases in the surgical lymph node specimens were found in seven (about 20 %) of the 35 patients in whom lymphadenectomy was performed. Four of the patients had their primary tumour in the area of the clitoris (2 with metastases on the right side and 2 with metastases on the left side), and three on one side of the labia majora or minora pudendi, and with ipsilateral metastases in the groin. In one of the patients with metastatic nodes on the left pelvic wall, the pelvic nodes were removed, however, not radically removed. The patient had an incorrect primary classification of her disease. A lymph node of about the size of an almond was found in the left groin, but was considered as merely being due to inflammation. She lived a year-and-a-half following completion of treatment, though with regional and local progression of tumour. In one patient there were regional metastases concomitant with a local tumour recurrence.

Two of the 28 patients without metastatic tumour growth in the excised lymph nodes (i.e. about 7 %) later disclosed metastases in the inguinal regions. It

was at the same time found that local recurrence had occurred in these two patients.

Eight of the 43 patients (about 19 %) who underwent radical vulvectomy, without additional lymphadenectomy, later disclosed metastases in the groins. In three of these patients there were simultaneous local tumour recurrences. Four of these patients had the lymph nodes irradiated with an absorbed target dose of 17.6-21 Gy, but the other four had not had radiation therapy. Out of the 28 patients in whom no metastases were recorded 25 received an absorbed target dose of 17.6 Gy, three patients had no irradiation of the inguinal regions. Out of seven patients in whom metastases were recorded, five were given additional irradiation with an absorbed target dose of about 19.2 up to 26 Gy, two patients did not receive additional irradiation.

Table II. Point-score values in relation to death in carcinoma, lymph node involvement and recurrences.

Total point-score values	No. of patients	Lymph node metastases with primary treatment	Local recurrence	Regional recurrence	Death in carcinoma ≤ 5 years
8	2	-	-	-	-
9	5	-	-	-	-
10	4	-	-	-	-
11	13	-	-	-	-
12	15	1	4	2	-
13	6	2	-	-	-
14	9	-	4	4	4
15	5	-	1	1	1
16	2	2	1	2	1
17	4	-	1	-	-
18	4	-	1	1	1
19	5	1	2	1	1
20	1	-	1	-	-
21	2	1	-	-	-
22	-	-	-	-	-
23	-	-	-	-	-
24	-	-	-	-	-
Total	77	7	15	11	8

In Table II five-year survival, lymph node involvement and recurrences in relation to the total point-score values are shown.

The five-year crude survival for patients with varying degrees of tumour differentiation was 45 of 54 patients with well differentiated, 4 of 7 with moderately differentiated and 4 of 6 with poorly differentiated tumours. These differences are not significant. No differences were seen in frequency of tumour recurrence and metastases between groups with different tumour differentiation. Further from the point-score values it was not possible to divide the material into various patient groups with different prognoses. There was, however, a positive correlation between local recurrences and scoring values ($p < 0.03$).

Multivariate analysis of the different parameters used in the point-score values showed the mode of invasion was to be the most important one ($p < 0.001$). Six local recurrences (about 12 %) were reported among the 49 patients with a score of one point and ten local recurrences (about 30 %) where the patients had a score of at least two points.

Among the seven patients with lymph node metastases the separate point-score value for vascular invasion was at least two points (implying a high suspicion for vascular invasion).

DISCUSSION

The initial symptoms of vulvar carcinoma are often mild and therefore ignored by the patient. A long history of disease prior to diagnosis implies a poorer prognosis, as the tumour is then at an advanced stage of progression. The survival rates in the present material are about the same as those reported by other authors (Wharton et coll 1974, Green 1978, Andreasson et coll 1980, Iversen et coll 1981).

There are conflicting opinions whether tumours in the clitoris area are more aggressive than in other locations and having a poorer prognosis (Rutledge et coll 1970, Parker et coll 1975, Friedrich & Di Paolo 1977, Piver & Xynos 1977, Magrina et coll 1979, Andreasson et coll 1980). The present series of stage I tumours and another larger material including stages I-IV tumours (Simonsen 1983) have shown only slightly poorer prognosis and a slightly higher rate of recurrence and metastases for tumours near the clitoris. It is probable that tumours located in the midline can spread to one or both sides of the inguinal regions. Metastasizing from unilateral tumours to the contralateral groin has not been recorded in this material. This agrees with several other reports (Karlgren 1977, Morris 1977, Iversen 1981), although

metastasizing to the contralateral groin has been noted in some other studies (Way 1960, Edsmyr 1962).

The importance of radicality at surgery of the primary tumour is evident from the figures of recurrence rates, which were considerably higher (8/20) among patients operated upon non-radically or with doubtful radicality than among those initially submitted to radical excision of the primary tumour (10/66). This is in line with previous findings.

Metastases in the regional lymph nodes were found in 8/43 (about 19 %), 2/28 (about 7 %) and 1/6 following different modes of therapy such as irradiation therapy alone, preoperative irradiation where no metastatic growth was found in excised tissues or pre- and postoperative irradiation in cases where radical surgery had demonstrated metastatic growth in the groin lymph nodes. The material is small and the patient groups included (i e only radiation treatment or irradiation in combination with surgery) are not strictly comparable.

Radiation therapy alone does not, however, give satisfactory results with the patient selection and with the absorbed doses used in this study.

In the present material moderately and poorly differentiated tumours did not have significantly poorer prognoses than well differentiated. No important differences were seen in regard to local and regional treatment failures, either. This agrees with most reports in the literature (Parker et coll 1975, Magrina et coll 1979, Iversen et coll 1981), although a significantly poorer prognosis for poorly differentiated tumours has also been suggested (Way 1960).

Several reports (Wharton et coll 1974, Parker et coll 1975, Magrina et coll 1979, Iversen et coll 1981) have suggested that carcinoma on the vulva with less than 3-5 mm depth of invasion and without vascular channel involvement, very rarely have lymph node metastases.

Poorer prognosis could not be demonstrated with an increasing number of points in the scoring system. This contradicts the findings of Kabulski & Frankman (1978), where there was poorer prognosis with an increasing number of scoring points. When we could not reproduce this figure the reason could be that we have only examined stage I carcinomas with a generally good prognosis. The frequency of inguinal metastases did not increase with increasing numbers of points, either. There were, however, more recurrences in patients

with high scorings, no patient with a point-score value less than 14 points died of the disease before 5 years and no patient with a point-score value less than 12 points had lymph node metastases with the primary treatment or later disclosed recurrences. In comparison it would appear, however, that the degree of radicality at surgery is the more important parameter for the treatment of the primary tumour.

CONCLUSIONS

Radical vulvectomy is the optimal form of treatment for the primary tumour. Reoperation should be considered if the initial measure has been non-radical or of doubtful radicality.

Ipsilateral groin lymph node dissection is sufficient for tumours limited to one side of the vulva. Midline tumours require bilateral groin dissection. Pelvic lymphadenectomy is not indicated.

The not very aggressive radiation therapy of the groins that has been used in this material is not sufficient as the only mode of treatment.

The methods of selection, the grading of tumour differentiation and the point-score system used in this study do not enable working out differentiated treatment schemes.

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Obstetrics and Gynecology (Submitted for publication)

BASAL CELL CARCINOMA OF THE VULVA

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SUMMARY

A clinical and histopathologic study of material from a series of 21 patients with basal cell carcinoma treated from 1960 until 1979 are reviewed. In 3 patients "mixed" tumour was recorded.

The histopathologic diagnosis: basosquamous carcinoma and the behavior of this carcinoma is discussed.

The mean age of the patients was 76 years. Presenting symptomatology consisted primarily of bleeding, burning or itching and ulcerations.

No cases of pure basal cell carcinoma gave metastasis to the regional lymph nodes, in no cases the cause of death could be said to be directly attributable to this kind of lesion.

Conservative approach consisting of wide local excision is suggested.

INTRODUCTION

Basal cell cancer is the most common type of skin cancer; it accounts for approximately 65 per cent of all cutane carcinomas. Ninety per cent are localized above the clavicle. The reported incidences of basal cell carcinomas in relation to other malignancies of the vulva vary from 0-13 per cent (1-3, 5-12), in most materials 2-3 per cent.

Temesvary (13) reported the first case in 1926, and since then many cases have been described. Many of the reports are sporadic case histories, describing one or two patients and many cases were merely tabulated in large series including all types of vulvar carcinomas. In 1979, Zerner and Fenn (12), after a survey of the literature, were able to perform data analysis in a total of only 90 reported cases. The aim of this paper is to give a general outline of basal cell carcinoma of the vulva, and to establish the best and least aggressive type of treatment.

MATERIAL AND METHODS

From 1960 until 1979, 317 patients suffering from invasive carcinoma of the vulva were treated at the Gynecologic Section, Department of Oncology, University Hospital of Lund. Twenty-one patients, including five treated outside the department, had received the histological diagnosis of basal cell carcinoma.

Table I. Case reports of 21 patients with basal cell carcinoma of the vulva showing size and location of the tumour, treatment and treatment failures.

Case No.	Age	Size of lesion (cm)	Location	Treatment		Local recurrence	Treatment of recurrence	Follow up
				Surgery	Radiation			
1	64	1x1	Clitoris	Local extirp	-	After 5 years left labia major	Local extirp	Living without evidence of disease 8 years after treatment.
2	71	1x1	Clitoris	Local extirp	21 Gy ¹³⁷ Cs to the groin	-	-	Living without evidence of disease 7 years after treatment.
3	74	2x2	Left labia major	Local extirp	-	-	-	Living without evidence of disease 5 years after treatment.
4	58	1x1	Clitoris	Local extirp	-	-	-	Living without evidence of disease 5 years after treatment.
5	80	3x3.5	Left labia major	Vulvectomy	-	-	-	Living without evidence of disease 3 years after treatment.
6	87	3x2.5	Left labia major	Vulvectomy	-	-	-	Died, 1.5 years after treatment; embolia pulm.
7	93	0.5x1	Left labia major	Local extirp	-	-	-	Living without evidence of disease 2 years after treatment.
8	57	1x1	Right labia major	Local extirp	-	-	-	Died in metastatic cancer colli uteri 2 years after treatment.
9	87	2x2	Right labia major	Local extirp	-	-	-	Living without evidence of disease after 1.5 years.
10	84	2.5x2	Clitoris	Vulvectomy	21 Gy ¹³⁷ Cs to the groin	-	-	Died 30 days after treatment; embolia pulm.

11	80	1x1	Left labia major	Vulvectomy	21 Gy ¹³⁷ Cs to the groin	-	-	Living 15 years after treatment without evidence of disease.
12	84	2x2.5	Right labia major	Vulvectomy	21 Gy ¹³⁷ Cs to the groin	-	-	Died in infarctus myocardi 7 years after treatment.
13	82	2x2.5	Right labia major	Vulvectomy	-	-	-	Died in infarctus myocardi 11 years after treatment.
14	79	4x3	Perineum anus	Vulvectomy	21 Gy ¹³⁷ Cs to the groin	After 4 years 5x2 cm perineum	Local extirp	Died in infarctus myocardi 5 years after treatment.
15	80	1x1	Right labia major	Vulvectomy	-	-	-	Living without evidence of disease 10 years after treatment.
16	73	1.5x1	Right labia major	Local extirp	-	-	-	Living without evidence of disease 12 years after treatment.
17	55	1.5x1.5	Left labia major	Vulvectomy	-	-	-	Living without evidence of disease 10 years after treatment.
18	76	2x2	Right labia major	Local extirp	-	-	-	Only six months observation time; living without evidence of tumour.
19	61	Multiple small lesions	Pubis Right labia minor	Vulvectomy	-	-	-	Living without evidence of disease 2 years after treatment.
20	73	2x2	Clitoris	Vulvectomy	21 Gy ¹³⁷ Cs to the groin	-	-	Died in infarctus myocardi 2 months after treatment.
21	70	2x1.5	Clitoris	Vulvectomy + groin lymphadenectomy	21 Gy ¹³⁷ Cs to the groin	-	-	Died after 2 years; lung metastasis.

In three patients, however, "mixed" tumour was recorded. In one patient with the diagnosis of malignant melanoma (Table I, Case 21), the histological examination of the specimen excised during radical vulvectomy showed areas of basal cell carcinoma.

In the other two patients there were observed in labia majora several areas suggestive of malignancy (Case 19). Biopsy from one area revealed squamous cell carcinoma, and from another area, basal cell carcinoma. In case 20 biopsy disclosed basal cell carcinoma, which in some areas showed an adenoid character. In some basally located tumour areas there was a squamous cell differentiation with the formation of pearls, with signs of keratinization, and with elongated nests and cords of tumour cells branching into the stroma which was infiltrated with inflammatory cells (Fig 1). The primary histopathological diagnosis was basal cell carcinoma with areas of spinocellular differentiation with a picture similar to squamous cell carcinoma. Several years later the diagnosis was revised as basal cell carcinoma with areas characteristic of adenoid and keratotic variants (3, 9).

These patients were classified as having malignant melanoma and squamous cell carcinoma, respectively, and have been treated in accordance with the usual therapy for these diseases.

The remaining eighteen patients were diagnosed as having pure basal cell carcinoma (Table I, Cases 1-18).

Age-distribution: The median and mean ages were 79.5 and 76, respectively, (range 55-90 years).

Symptoms and delays in seeking medical help: The most common primary symptoms were bleeding, burning or itching and ulcerations, or a combination of these symptoms. Six patients reported bleeding as the initial symptom, seven itching or burning, and five ulcerations. The time lapse from the first symptom until the patient sought medical help varied from 1 month up to 5 years.

The diameter of the vulvar tumours or ulcerations ranged from 0.5-4 cm (average 2 cm). Four tumours were localized to the clitoris and one to the perineum-anus. The others were localized to labium majora only, or in two cases, to both labia majora and minora. Right- and leftsided tumours have been found in the same frequencies. No metastases in the regional lymph nodes were recorded.

The treatment has been surgical. In eight cases, simple vulvectomy was performed. In the other cases, the surgical treatment varied from local extirpation to hemivulvectomy. In five cases, the surgery has been combined with prophylactic irradiation of the lymph nodes of the groin. A ^{137}Cs -unit was used with single field technique, a field size of 8×15 cm and SSD = 20 cm. The peak absorbed dose was 7 Gy per fraction, with three fractions per week and a total of 21 Gy. The observation period was 2-19 years.

RESULTS AND DISCUSSION

No cases of regional metastasizing have been reported during the observation period.

After four and five years, respectively, two patients showed local recurrences, which were successfully treated by local surgical extirpation.

One patient died in connection with primary treatment: hemivulvectomy + prophylactic irradiation of the groin regions. The patient died of pulmonary embolism 30 days after primary treatment.

None of the patients have died due to recurrence or progression of the disease during the observation period.

Vulvar basal cell carcinoma has been reported to be more prevalent in the white women than in Negro women (3, 8, 12). Its etiology is not known; chronic irritation, syphilis and arsenicals may be predisposing factors (2, 3, 6, 12). Previous irradiation has been asserted to be a predisposing factor in many reports (3, 5, 9, 12). In this report, three patients with carcinoma of the uterine cervix have been treated with external irradiation, and intrauterine and vaginal radium applications at 13, 6 and 4 years, respectively, before the basal cell carcinoma on the vulva occurred. The known relationship of associated leukoplakia and vulvar squamous cell carcinoma does not seem to be true for vulvar basal cell carcinoma.

The histologic pattern of these tumours generally resembles that of basal cell carcinomas occurring at other sites on the skin. Those occurring on the vulva are divided into several types, based on their clinical presentation.

The first one is the rodent ulcer type, which is sharply defined, burnished and grows laterally rather than deeply into the tissues; pigmentation may or

may not be present. The second type is a superficial basal cell or erythematous type in which no ulcer is present. The third type is the hypertrophic type. The surrounding connective tissues frequently show a chronic inflammatory cell infiltrate of varying severity.

Basosquamous carcinoma has been considered as a variant of basal cell carcinoma with a squamous cell component requiring more aggressive treatment (3, 9). Only in some few studies there are strict criteria for definition, relating basosquamous carcinomas as basal cell carcinomas with a malignant squamous cell component(s) (4). Using this definition cases of basosquamous carcinomas were found to be rare, and it seems reasonable to assume that a lot of basal cell carcinomas with a squamous cell component, diagnosed as basosquamous carcinomas, are probably the same as keratotic basal cell carcinomas or basal cell carcinomas with squamous cell metaplasia, which are a not uncommon variant (cf. the present case 20). Whether they should be treated differently have been disputed (6, 7).

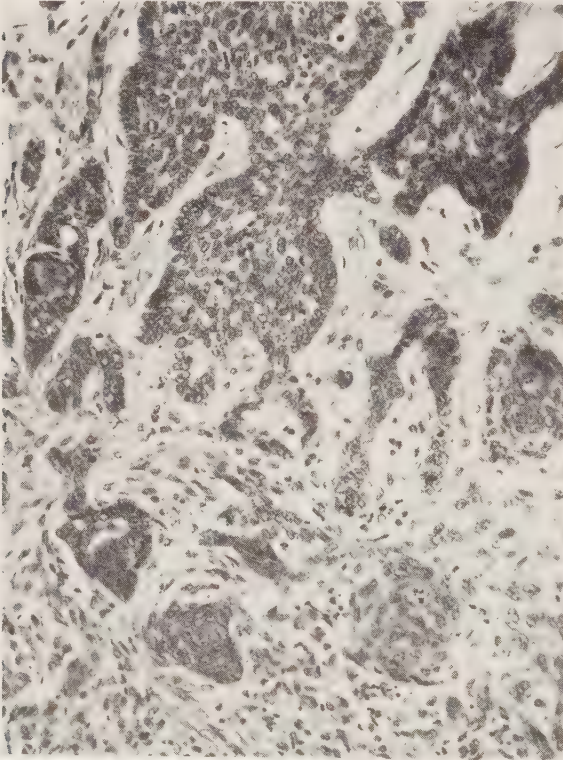


Fig 1.

Case 20, primarily diagnosed as basal cell carcinoma with areas of spinocellular differentiation compatible with squamous cell carcinoma. The diagnosis was later revised as keratotic basal cell carcinoma.

H and E. 175 x.

Case no. 5 in this material (Table I) was primarily diagnosed as a basal cell carcinoma with an aggressive mode of growth (Fig 2 and 3); this patient was treated with simple vulvectomy and has not shown any symptoms of local recurrence or metastasizing during the observation period (2.5 years).

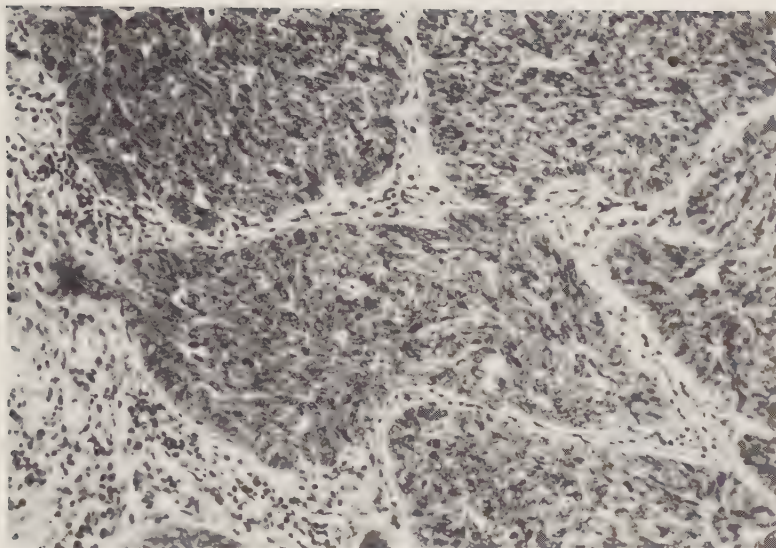


Fig 2. Case 5, diagnosed as basal cell carcinoma with an aggressive mode of growth. Upper part of the tumour consisting of solid tumour sheets with margins of palissading cells.

H and E. 170 x.

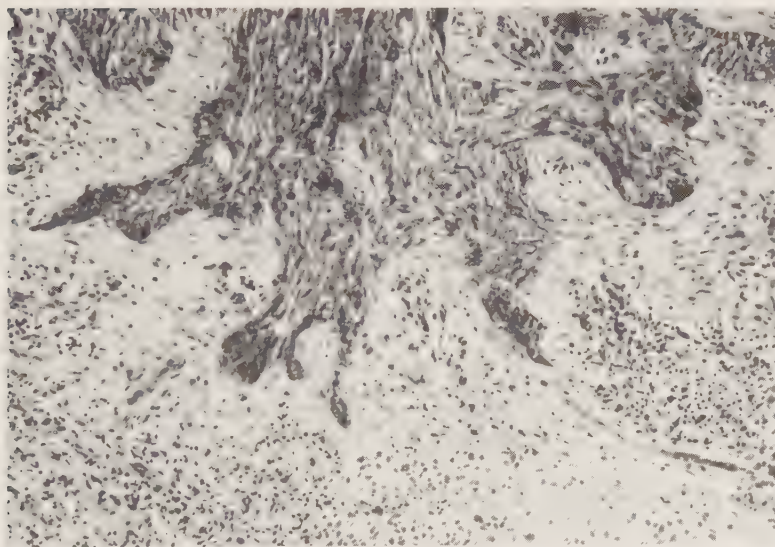


Fig 3. Case 5, basal part of the tumour with elongated strands splitting up into the surrounding connective tissue stroma which is infiltrated with inflammatory cells.

H and E. 130 x.

It would on the other hand seem to be highly probably that double carcinomas, not uncommonly seen (3) (2 cases of 21, ≈ 9.5 % in this material), are to be treated as prescribed for the most aggressive types of tumour, since the prognosis follows their pattern.

The patient with malignant melanoma died of pulmonary melanoma metastases two years after treatment. The patient with squamous cell carcinoma is still alive two years after treatment.

The literature shows no agreement on the metastasizing ability (2, 3, 6, 7, 9, 11, 12) of basal cell carcinoma. Vincent S Palladino (6) studied in relevant literature in 1969 and subsequently concluded that previously described cases of metastasizing basal cell carcinomas were not of pure basal cell type. Photomicrographs do not conclusively show that the tumour in lymph nodes is of the basal cell type. Recent reports (10, 12) have, however, described single cases of metastasizing basal cell carcinoma in the vulva. It seems, furthermore, well-documented that these tumours in other skin localizations do metastasize, although seldom (10).

Other tumours also occur quite frequently in this group of patients, in 10-20 per cent (3, 6). In this material, 4 out of 21 (≈ 19 %) had basal cell carcinoma in other sites, and 3 out of 21 (≈ 14 %) had carcinoma of the uterine cervix (squamous cell carcinoma).

Basal cell carcinoma has been described as a multifocally growing tumour, which appears to contribute to the high frequency of local recurrence.

Among 18 patients suffering from pure basal cell carcinoma, two local recurrences were reported during the observation period (2-19 years). Both recurrences appeared approximately five years after primary treatment, and in both cases local surgery was again carried out. It must be pointed out that these two patients represent two out of three patients primarily treated with surgery of histologically dubious radicality.

The treatment of choice has been discussed in many reports (2, 3, 6, 7, 9, 12). Considering the high frequency of postoperative mortality and morbidity in connection with radical vulvectomy including groin dissection, this approach does not seem rational (14). Very few cases have metastases to the regional lymph nodes, and in no case could the cause of death be directly attributable to this kind of lesion.

Radiotherapy, electro-cauterization or cryosurgery have been used, but are very seldom recommended today (2, 3, 12). Surgical treatment comprising local excision of depth- and lateral radicality using a scalpel, electrocautery knife or laser beam will be adequate treatment in more than 95 per cent of the cases of pure basal cell carcinoma of the vulva, and this treatment has a very low, postoperative mortality and morbidity rate.

CONCLUSIONS

Basal cell carcinoma in the vulva region is a rare disease and represents only 2-6 per cent of the total number of vulvar carcinomas, a type of carcinoma which rarely or never metastasizes. Squamous elements in basal cell carcinomas occur relatively frequently; this is a benign phenomenon with no effect on the prognosis.

Double carcinomas with malignant melanomas or squamous cell carcinoma growing in close proximity to the basal cell carcinoma occur frequently and have decisive prognostic significance.

Treatment with local extirpation of optimal radicality is an adequate curative treatment in cases of pure basal cell carcinoma. Poor radicality and/or multifocal growth increases the risk for local recurrence.

On account of the risk for local recurrence and the high frequency of several carcinomas in the same patient in this group, prolonged clinical control is recommended.

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Annales Chirurgiae et Gynaecologiae 71:334-339, 1982

THE RECOVERY PATTERN OF PATIENTS WITH VULVAR MELANOMA TREATED BY COMBINED SURGERY AND RADIATION THERAPY

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SUMMARY

Twenty-five patients with malignant vulvar melanoma have been treated with radical vulvectomy using the warm knife-open wound technique. Following pre-operative radiation therapy, dissection of the groin and, in some cases, pelvic lymphadenectomy, were performed as a second procedure.

Crude five-year survival was 9/21 (~43 %). Patients with tumours of Clark level II-IV have been found to have a good prognosis (7/9), while those with Clark V-tumours have had an extremely poor prognosis (2/10). Prophylactic dissection of the inguinal nodes has not been found to improve the prognosis, and pelvic lymphadenectomy is considered to be inadvisable.

INTRODUCTION

Malignant melanoma of the vulva constitutes only 0.05-0.5 % of all the forms of malignancy occurring in the female genital organs (4). It is, after squamous cell carcinoma, the most frequent form of vulvar tumour; about 3-7 % of the malignant melanomas in women are confined to the vulvar region (3, 12, 15, 18, 21). Vulvar melanomas do not differ histologically from melanomas in other regions of the body and the metastatic localizations are also identical (5, 11).

This study has been done to account for the recovery pattern of patients with malignant vulvar melanoma when treated with combined surgical and radiation therapy.

MATERIAL AND METHODS

The material consists of 25 patients with malignant vulvar melanoma treated during the years 1960-1979 in the Gynecologic Section, Department of Oncology, University Hospital, Lund, Sweden. The receiving area is restricted to an area in the southern part of Sweden with about 1 200 000 inhabitants.

The melanomas in this material represent 8.5 % of all the malignant vulvar tumours treated during this period of time. The mean age in the group was 66.8 years (range from 36-86 years); only four (16 %) patients were under 60 years of age.

Classification according to the FIGO Staging System (10) resulted in 12 patients in stage I, 4 in stage II, 5 in stage III and 4 patients in stage IV.

In eight patients, the tumour was located in the region of the clitoris, in two of these cases involvement of the meatal urethra was demonstrated. In seven cases the tumour site was the labium majus and in six cases the labium minus. Four tumours involved both labia majus and minus.

At histopathological re-examination of the biopsies and surgical specimens, classification was performed according to that of Clark (5). The pathologist who did this classification did not have access to the medical records of the individual patients.

Clark et al's system is based on the inverse relationship between survival rates and level of infiltration in cases of cutaneous melanoma. Tumour infiltration is classified in the following manner:

- Level I: Tumour cells confined to the epidermis.
- Level II: Tumour cells extending into the papillary portion of the dermis.
- Level III: Tumour cells filling the papillary dermis and "pushing" down upon the reticular dermis.
- Level IV: Tumour cells extending into the reticular dermis.
- Level V: Tumour cells extending into the subcutis.

The patients have been treated with combined surgery and radiation therapy. Radical vulvectomy utilizing electroresection with the wound left open has been performed on 22 patients, and external radiation was applied to the inguinal regions in connection with surgery. A ^{137}Cs -unit was used with single-field technique, a field size of 8×15 cm and SSD=20 cm. The peak absorbed dose was 7 Gy per fraction, with three fractions per week and a total of 21 Gy. Six weeks after termination of external irradiation, bilateral inguinal lymphadenectomy was carried out in patients who clinically and technically could be subjected to surgery (16 patients). This operation was supplemented with pelvic lymphadenectomy in three patients where macroscopic examination had revealed metastatic nodes. When metastatic nodes were detected microscopically after surgery (five patients), the inguinal region and pelvic wall nodes on the side in question were given external irradiation using a ^{60}Co -unit with single-field technique and SSD=80 cm. The peak absorbed dose was 3 Gy per fraction, five fractions per week, up to a total peak absorbed dose of 24-33 Gy, depending on the findings in the surgical specimens.

Three patients with advanced tumour growths (FIGO/Clark III/IV, III/V and

IV/V) received only palliative treatment.

Treatment failures registered in the perineum, the vulva, the lower half of the vagina or in the urethra have been classified as local recurrences. Metastases to the groin and/or the pelvic walls after completion of treatment have been defined as regional metastases. When spreading to organs above the pelvis has been detected, it has been defined as distant metastases. The patients were not grouped according to progression of residual tumour or recurrence. Prognosis has been expressed in terms of two- and five-year tumour mortality and by survival rate using the lifetable technique.

Survival rate, %

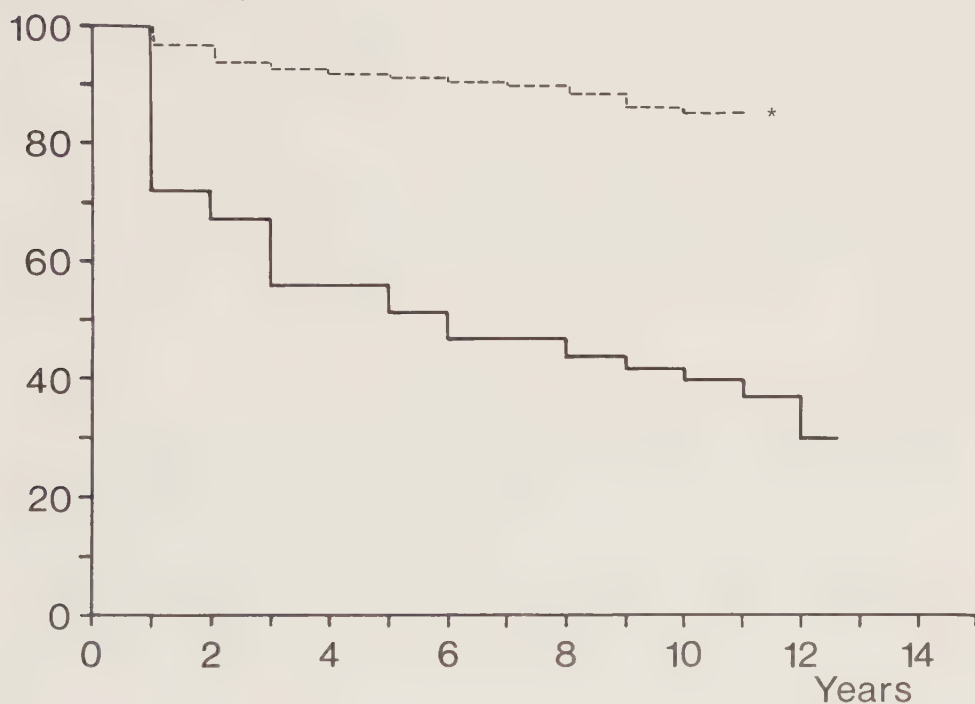


Fig 1. Survival curve based on the lifetable technique for 25 patients with malignant melanoma of the vulva. *General population.

FIGO

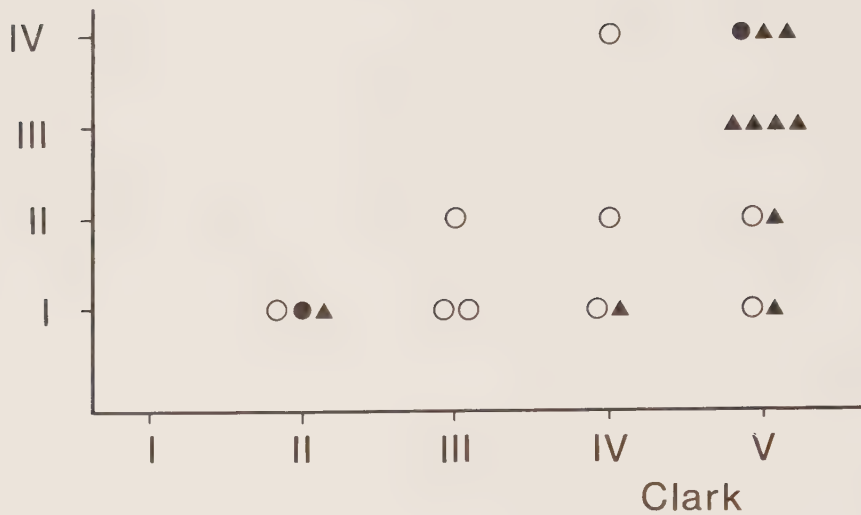


Fig 2. Prognosis, FIGO-staging and Clark-classification five years after completion of treatment. O Alive and with no evidence of disease. ● Dead of intercurrent disease. ▲ Dead of tumour.

RESULTS

Twelve (~48 %) of the 25 patients treated during this twenty-year period have died of cancer with a median survival of ten months. Two-year and five-year crude survival rates were 15/23 (~65 %) and 9/21 (~43 %), respectively.

Six patients have died of intercurrently occurring disease without signs of residual tumour at 0.5, 2.5, 8.5, 10.5, 11.0 and 14.0 years following the conclusion of treatment. The survival curve based on life-table technique is presented in Fig 1.

Fifteen of 23 patients were free from cancer after two years' observation. As mentioned above, three patients with advanced tumour were only treated palliatively (radiation therapy and melphalan) and died from their disease during the first year following treatment.

Surgical intervention, operative findings and radicality of surgery as well as type of treatment failure are given for the entire group in Table I.

Eight of nine patients with five-year survival were submitted to a radical,

therapeutic operation of the primary tumour. One patient had local recurrence of her disease 3.5 years after an initial operation of doubtful radicality and was re-operated on. Groin dissection was performed in seven patients; the extirpated lymph nodes appeared normal in all cases.

Five of the ten patients who succumbed from their disease within five years following therapy had had radical operation of the primary tumour and the regional lymph nodes had shown no evidence of metastases. Three of these five patients had local recurrences later on, and two of them died with regional and distant metastases. All of the four patients who had involvement of the inguinal nodes died within two years. Two of them also had distant metastases.

The correlation between prognosis on the one hand and FIGO/Clark classification on the other is shown for 21 patients with five years' observation in Fig 2.

The eight patients with involvement of the clitoris were classified according to Clark: 4 patients Clark V, 2 patients Clark IV, 1 patient Clark III and 1 patient Clark II. The patients who survived for more than five years have tumours with Clark IV and V.

Eight of sixteen patients treated with radical or doubtfully radical surgery of the primary tumour who either were observed five years or expired from their disease within the five-year period were classified as Clark II-IV. Seven of these eight patients survived five years or longer and one patient died of inextirpable, local residual cancer followed by generalization of the disease. Six of the eight patients classified as Clark V died with generalized disease, one of whom had local recurrence.

No deaths have been recorded either at surgery or during the postoperative period. The operation area was infected in two cases, and one case of vaginal stricture was reported. Moderate lymphoedema of the lower extremities occurred in three patients following lymphadenectomy.

Table I. Case reports of 25 patients with malignant vulvar melanoma showing type of operation, surgical findings and type of treatment failure.

No.	Type of operation	Radicality	Local recur	Regional metast	Distant metast	Survival (years)	Clark	Died from
1	Vulvectomy Groin diss Pelv lymphad	Radical perigland perigland	-	-	-	1	3	
2	Vulvectomy	Doubtful	-	-	-	3	4	
3	Vulvectomy Groin diss	Radical no tumour	-	-	-	4	4	
4	Vulvectomy Groin diss	Radical no tumour	-	-	-	10	4	
5	Vulvectomy Groin diss	Radical no tumour	-	-	-	15	3	
6	Vulvectomy Groin diss	Radical no tumour	-	-	-	15	3	
7	Vulvectomy Groin diss	Radical no tumour	-	-	-	16	5	
<u>Intercurrent diseases</u>								
8	Vulvectomy	Doubtful	-	-	-	$\frac{1}{2}$	3	Pulm embolus (autopsy)
9	Vulvectomy	Radical	-	-	-	$2\frac{1}{2}$	2	Carcinoma of colon
10	Vulvectomy Groin diss	Radical no tumour	-	-	-	$8\frac{1}{2}$	4	Gastric cancer
11	Vulvectomy Groin diss	No tumour	$3\frac{1}{2}$ years reop	-	-	$10\frac{1}{2}$	3	Cerebral haemorrhage
12	Vulvectomy	Radical	-	-	-	11	4	Cerebral haemorrhage

13	Vulvectomy Groin diss Pelv lymphad	Radical no tumour no tumour	-	-	-	14	5	Myocard infarction <u>Melanoma</u>
14	Radiother (pall)		Progressive disease			<½	5	
15	Local excision		Progressive disease			½	2	Generalized (autopsy) disease
16	Radiother (pall)		Progressive disease			1	5	
17	Vulvectomy Groin diss	Radical Perigland	-	Progressive disease		<½	5	
18	Vulvectomy Groin diss	Doubtful Radical	-	Progressive disease		½	5	Generalized (autopsy) disease
19	Vulvectomy Groin diss	Radical Radical	-	5 months	5 months	<1	5	
20	Vulvectomy Groin diss Pelv lymphad	Not radical Perigland Perigland	6 months	6 months	6 months	<1	5	
21	Vulvectomy	Radical	-	-	9 months	<1	5	
22	Vulvectomy Groin diss	Radical no tumour	6 months	6 months	-	2	5	
23	Vulvectomy Groin diss	Radical no tumour	-	-	1½ years	2	5	Locally treated generalized (autopsy) disease
24	Vulvectomy Groin diss	Radical no tumour	2 years	4 years	4 years	4	4	Brain, lung, liver (autopsy) metastases
25	Vulvectomy	Radical	4½ years	-	-	5½	2	Vagina, liver, bone (autopsy) metastases

DISCUSSION

Five-year survival was attained in about 43 % of the patients in the present material, which agrees well with the reports from other treatment centres (25-50 %) (3, 5, 9, 11) and corresponds to the survival rates for malignant melanoma in other sites of the body.

The prognosis for tumours involving the clitoris region is usually considered quite poor due to the fact that the lymphatics from the clitoris drain directly into the pelvic nodes. This viewpoint seems to be supported by the present investigation: six of the eight patients with involvement of the clitoris died from their disease within five years following treatment.

The importance of the degree of radicality used at surgery is clearly demonstrated by the prognostic figures of this study, and by many other authors in the literature (3, 12, 15, 21). Local excision of malignant melanoma of the vulva is clearly inadequate, and if this has been done as a primary measure it should be followed by radical vulvectomy. Chances of cure are higher if surgery is performed within 1-2 weeks following diagnosis (13, 14).

Table II. Prognosis and classification according to Clark.

Clark class	Clark et al.	Chung et al.	Present material
II	8.3 %	0 %	20 %
III	35.2 %	60 %	
IV	46.1 %	60 %	25 %
V	52.0 %	80 %	73 %

Different histological staging systems have been developed in order to define the degree of malignancy of melanoma: direct measurement (Breslow, 2), measurements of the depth of invasion by histological landmarks (Clark, 5) and the combined microstage technique (Chung, Wanabe, 3, 21). In this study, the Clark Classification System has been used. The correlation between prognosis and the Clark levels can be seen in Fig 2 and Table II. Clark V points towards a clearly poor prognosis, which corresponds to the findings of other investigators (3, 4, 18, 21). Clark IV-tumours do not, on the other hand, have as poor prognosis as other studies have reported (3, 4). However, a much larger series would be necessary to make any definite evaluation of the prognostic effects of tumour classification systems.

If Clark classification and radical surgery are used as the basis for a prognostic selection method, only one of the eight patients classified as Clark II-IV died of the disease within five years. Of the patients classified as Clark V who underwent similar surgery, six out of eight died within five years. Clark V-tumours are characterized by regional and distant metastases.

Pre-surgical irradiation with a peak absorbed dose of 21 Gy given in three fractions over five days has been the initial treatment given to the regional lymph node areas. This dose-fractioning method was adapted due to limited treatment facilities and for technical reasons. It is considered to be adequate due to the radiobiological pattern of the malignant melanomas, especially their characteristic cellular survival curve, and is also very similar to those currently used for the irradiation of malignant melanoma (6, 17, 20). No evaluation of the tumouricidal effect of irradiation can be made on the basis of this material, however, as surgical intervention comprised groin dissection and, in some cases, pelvic lymphadenectomy. All of the patients who had tumours in regional lymph node areas have died of their disease, which is consistent with the findings of other authors.

Radical vulvectomy and bilateral inguinal dissection are at present the usual surgical treatment for malignant melanoma, and this general principle is reflected in current gynecological and surgical literature. Morrow and Di Saia (12) have, for example, stated that "the minimum acceptable treatment for vulvar melanoma, irrespective of the lesion size or depth of invasion, is radical vulvectomy and bilateral groin (inguinal and femoral) lymphadenectomy done in continuity". Radical vulvectomy utilizing electro-resection has been used in the present material. This technique is less traumatic for the more aged and weaker patients. Dissection of the groin was done as a second phase. This two-stage surgery did not lead to any per- or postoperative deaths in this series nor in a larger group of patients with malignant tumour in the vulva (19). No disadvantages have been found, and the technique seems to be superior to one-phase surgery, which has an appreciable mortality rate (about 5 %) (1, 7). The role of pelvic lymphadenectomy has not yet been precisely established (8). Some authors (12, 16, 22) are of the opinion that pelvic lymphadenectomy should be done routinely. Other recent studies on malignant melanomas do not substantiate even prophylactic lymphadenectomy (11, 13, 14). Surgical measures seem unnecessary in cases where no metastases to the lymph nodes can be detected. While in patients with confirmed metastases there was no cure.

CONCLUSIONS

Malignant melanoma of the vulva is an aggressive tumour disease. Radical vulvectomy performed on Clark II-IV tumours improves the prognosis considerably. Patients at Clark V-stage disease have an extremely poor prognosis and tend to die from rapid distant spread of the condition. Prophylactic dissection of the inguinal nodes has not been found to improve the prognosis and pelvic lymphadenectomy is considered to be inadvisable.

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Gynecologic Oncology (Accepted for publication)

RADICAL VULVECTOMY WITH WARM KNIFE- AND OPEN WOUND-TECHNIQUE IN VULVAR MALIGNANCIES

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SUMMARY

Radical vulvectomy using warm knife- and open wound-technique was performed as the first step in a two-phase surgical approach in 274 patients with malignant vulvar tumours. Crude 5-year survival was registered in 133/223 (60 %) patients. The complication rate was low and the hospitalization period short (mean 16 days).

INTRODUCTION

Prior to 1940, carcinoma of the vulva was not well understood. Treatment in the most advanced centres was ususally not effective, with 5-year survival rates of 10-20 %.

Taussig (1) was one of the first to advocate treatment by radical vulvectomy with resection of the regional lymph nodes. He evaluated 155 patients with carcinoma of the vulva, 68 of whom had been operated ad modum Basset. With this technique, an over-all 5-year survival rate of 58.5 % was achieved. For the past 40 years, the most widely accepted therapy for carcinoma of the vulva has been radical vulvectomy with inguinal and pelvic lymphadenectomy. Way (2) established that the survival was related directly to a wide and deep removal of the vulva coupled with an aggressive attack on the regional lymph nodes.

The aim of this paper is to evaluate radical vulvectomy with warm knife- and open wound-technique as the first step in a two-phase surgical approach to the treatment of malignant vulvar tumours.

MATERIAL AND METHODS

During the period 1960 to 1979, 317 patients with the diagnosis malignant, invasive tumour of the vulva were referred to the Gynecologic Section, Department of Oncology, University Hospital, Lund.

The distribution among the various stages (FIGO) was the following: Stage I: 111 (35 %), Stage II: 80 (25 %), Stage III: 82 (26 %) and Stage IV: 44 (14 %). The TNM (UICC) classification was used to define the local spread of the tumour (3). The histologic distribution of the material is shown in Table I. The mean age was 64 years (16-96 years). Median age was 69.5.

Table I. Histopathological findings in 317 patients with malignant vulvar tumours.

Squamous cell carcinoma	264
Malignant melanoma	25
Basal cell carcinoma	14
Mb Paget	4
Mb Bowen	2
Anaplastic cancer	2
Adenocarcinoma	2
Adenosquamous cancer	1
Lymphoma	1
Rhabdomyosarcoma	1
Leiomyosarcoma	1
Total	317

Radical vulvectomy using warm knife-technique was performed on 274 patients and the evaluation of the surgical method is based on this material. Forty-three patients were excluded from this study. Due to old age, poor general condition and advanced disease, 25 patients had received only palliative treatment. Fifteen patients with the diagnosis basal cell carcinoma or extremely early squamous cell carcinoma had undergone partial vulvectomy; three patients refused treatment.

In 145 cases, groin dissection was performed. In 31 of these cases, pelvic lymphadenectomy was also performed. Fifteen patients received preoperative radiotherapy on the primary tumour in order to reduce tumour mass and render it technically operable.

Using warm knife-technique, vulva was removed with its underlying subcutaneous tissues and muscles. The medial limit of the dissection was the hymenal ring, leaving the urethra intact. The lateral limit was the labio-crural fold crossing the perineum above the anus caudally and mons veneris cranially with the intended minimum free margin to the tumour of 2 cm. Individualization of the resection line, however, was sometimes necessary in the patient material studied here because of the localization and extent of the tumour. The excision was done to the deep fascia. Sometimes excision of parts of the urogenital diaphragm and distal part of the urethra as well as dissection of paravaginal and ischorectal spaces was done. The blood vessels were

coagulated. After removal of the operation specimen, the wound surfaces were diathermically coagulated, partly to stop the bleeding and partly to destroy the tumour cells contaminating the operation area. The wound was left open for secondary healing.

A Dextran solution with penicillin and boracic vaseline were applied alternatively during the initial ten days for the treatment of the local wound and subsequently only boracic vaseline was used. An indwelling catheter was installed for 3-5 days.

During initial postsurgical care, and irrespective of the palpation findings, preoperative radiotherapy was given to both groin regions. Lymphadenectomy was performed six weeks later if the general condition of the patient so permitted. If this was not the case, extended radiotherapy was applied. Pelvic lymphadenectomy was performed in cases where a clinical examination revealed suspicious metastases of the inguinal lymph node stations. External radiotherapy was applied postsurgically in cases where metastases had been detected in the groin or pelvic lymph nodes.

The surgical intervention was defined as radical if the distance from the microscopic tumour to the wound edge was >1 cm; ≤ 1 cm was defined as dubious radicality and tumour in the resection edges as not radical.

Treatment failures registered in vulva, perineum, lower half of vagina and urethra have been classified as local recurrences. Recurrences in the area between the vulva and the groins have been recorded separately. Local recurrence registered within six months after primary treatment has been defined as progressive disease. The length of the postoperative hospitalization period as well as postoperative complications and sequelae have been recorded. Patients who have died within five years from cancer and intercurrent diseases have been recorded.

RESULTS

There was no record of deaths during operation or postoperative care in this material. The mean hospitalization period for vulvectomy was 16 days (5-45).

The patients suffered no wound pain for the first 3 to 4 days. Normal wound pain was registered in the following period. The patients were fully mobilized

the day after operation, and, as a rule, no parenteral nutrition was necessary. Wound healing with secondary granulations was completed within 6-8 weeks (Fig 1a, b, c). Postoperative bleeding of $>\frac{1}{2}$ l was registered in nine cases. Wound infection necessitating administration of antibiotics was observed in nine patients. In two, extensive necrosis of the operation area was seen. One case of pubic osteitis which in less than six weeks responded to antibiotic treatment and left no permanent injury was registered. Incontinence was observed in one case where resection of almost half the urethra was performed in connection with the vulvectomy. Vulvar stricture was frequent following vulvectomy. In 12 patients this caused complaints necessitating correction of the stricture. Five patients suffered from prolapsus following the operation. One postoperative case of vesico-vaginal fistula was reported. Four thromboses of the lower extremities and one pulmonal emboli were observed.



Fig 1a. Vulva carcinoma before surgical treatment.



Fig 1b. The vulva area after radical vulvectomy; the wound has been left open for secondary healing.



Fig 1c. The vulva area eight weeks after surgery.

The surgical intervention was radical in 181 cases, dubiously radical in 48 and not radical in 45 cases. The surgical radicality determined by the site and extension of the primary tumour is shown in Tables II and III. The surgical radicality was less pronounced in cases with extensive tumour growths and tumour infiltration in extra-vulvar tissue.

Table II. Operative radicality in different stages (FIGO).

No. of patients	Stage	Radical		Doubtful radicality		Not radical	
		No.	%	No.	%	No.	%
97	I	78	80	13	14	6	6
75	II	51	68	15	20	9	12
76	III	44	58	15	20	17	22
26	IV	8	31	5	19	13	50

Table III. Operative radicality in different locally advanced tumours (UICC).

No. of patients	"T"	Radical		Doubtful radicality		Not radical	
		No.	%	No.	%	No.	%
115	1	93	81	14	12	8	7
108	2	66	61	24	22	18	17
47	3	22	47	10	21	15	32
4	4	-	-	-	-	4	100

Among 274 operated patients, 63 (23 %) local treatment failures have been recorded, progressive disease in 21 patients and recurrences in 42. Non-radical, initial surgery was performed in 20/63 patients (32 %) and 13/63 (21 %) were given surgery of dubious radicality. 3/63 local treatment failures were determined, localized in the skin-bridge between the vulva and the groin area. For patients with local recurrences and local progressive disease, the prognosis was poor.

16/20 patients not radically operated, 10/13 operated with dubious radicality and 12/30 patients radically operated died of the disease within five years.

Of 223 patients with a minimum of 5 years' observation, 67 died of their disease and 23 patients died of intercurrent disease. Crude 5-year survival was 60 %.

DISCUSSION

The radical vulvectomy first described by Taussig and Way (1, 2, 4, 5) also comprises groin dissection. In the last 30 years, many reports have described modifications of the technique of the primary operation (6-14). Locally advanced vulvar cancer - UICC-classification T_3 , T_4 and N_3 - represents a difficult management problem. In 1956, a therapeutic alternative was introduced by Brunschwig and Daniel (6), who were the first to publish experience of exenterative surgery in advanced vulvar cancer. In recent years several series describing surgical results of cancer of the vulva include some type of pelvic exenteration in 10-20 % of the patients (6, 7, 8).

High rates of wound break-down, local sepsis, prolonged hospital stays, pelvic relaxation and operative mortality have accompanied this aggressive surgical approach. Operation time of approximately 4-5 hours or more is normal (15, 16). Wound infection and dehiscence have been reported with an incidence that varies from 20 to nearly 60 % (17). Postoperative hospital stay of 40 to 60 days is not uncommon (5, 18). Pelvic relaxation is a long-term complication with an incidence of 4-24 % (19).

Operative mortality is parallel to the aggressivity of the surgical approach. At radical vulvectomy it is 1-3 % (8), at radical vulvectomy and groin lymphadenectomy it is 5-10 % (18, 20), and at pelvic exenteration it is 6-25 % (8, 16, 21). Postoperative complications are so common that their absence has sometimes been considered indicative of incomplete operation.

In an attempt to reduce postoperative complications, various modifications of the surgical technique have been introduced. A modification of the classical line of incision is described by M.M. Abitbol (11) as a line of incision which leaves a major part of the mons veneris in place and approaches the perineum in a butterfly shape. Open wound-technique was used by James Daly (12). Preoperative radiation therapy six weeks prior to radical surgery has been described by Annibel A. Acosta (13). Different types of myocutaneous grafts used in primary operation as well as secondary reconstruction of the vulva have been reported (22, 23, 24). These reports, as well as a gradual modification of the initially described technique (Way), seem to indicate

that a reduction of the postoperative complications is possible without reducing the impressive survival figures demonstrated in many reports (6-8, 10-14, 26).

In Europe, the aggressive surgical approach with its high morbidity and mortality rates has not yet been accepted by all centres. Radical electro-coagulation of the entire vulva area was described by Berven in 1922 (25), and this method has with some modifications been used in several Scandinavian centres. This method combined with radiation of the lymph node stations in the groin and pelvic regions, with or without surgical lymphadenectomy of the groin and pelvic nodes, has resulted in acceptable 5-year survival rates with low morbidity and mortality in connection with the treatment (26, 27).

As a consequence of the age of the patients included in this material (median 70 years), as related to the median of the majority of the other reports (53-63 years), the surgical procedure has been split into two relatively short operations. The average length of the operation for radical vulvectomy using warm knife-technique was 35 minutes, and for groin dissection 80 minutes. By applying open wound-technique in connection with vulvectomies, postoperative infections are avoided to a great extent, and the problem of skin necrosis is eliminated. The cosmetic result is satisfactory. Open wound-technique, however, is considered less applicable in cases of extensive tumour growth covering large areas including abdominal and gluteal regions, as a consequence of scar formation during secondary healing.

The average hospitalization was short (16 days for vulvectomy and the same for groin dissection). No death was recorded during or immediately following operation and/or hospitalization. Complication frequency was relatively low, only stricture of the introitus vaginae, which is a risk in all kinds of vulvectomy (10-30 % in various reports), was frequent. As a consequence, younger women should be instructed to use e.g. a plexiglass cylinder to widen the introitus vaginae during healing.

Local treatment failure has been recorded in 23 %, a result that is consistent with the results of other materials (11, 13, 15, 25). Only about 5 % of the recurrences were restricted to the skin area between the vulva and the groin regions. The two-phase surgical approach, eliminating extirpation of a skin-bridge between the vulva and groin regions, is therefore considered to not increase the risk for treatment failure.

The significance of radical surgical intervention is clearly shown in this material. Local treatment failure was registered in 17 % following radical surgery and in 34 % following dubiously radical or non-radical surgical intervention. Similar frequencies have been reported by other investigators (13, 20, 28).

The difficulty associated with radical surgery is augmented with the extension of the tumour growth (radical in 81-61-47-0 % in T₁₋₂₋₃₋₄, respectively (UICC). Identification of the resection limits in connection with the radical vulvectomy is a complicated surgical problem. Thirty-eight (60 %) of the 63 patients with a clearly defined local treatment failure died of their disease within five years; 26 (≈79 %) of 33 had been operated with unsatisfactory radicality or no radicality; 12 (≈40 %) of 30 with satisfactory radicality. Extremely poor prognosis was registered for local treatment failure debuts within six months - i.e. progressive disease, see Table IV. This rapidly appearing treatment failure is seen to be indicative of a very aggressive tumour disease. A totally different pattern is seen in local treatment failures detected more than six months after surgery. Only six of 24 patients in this category died of the disease.

Crude survival (60 %) coincides on the whole with the results of other reports (1, 2, 5, 8, 10, 18, 20) of similar stage-distribution, in spite of the high median age of the patients in the present material.

Table IV. Prognosis and operative radicality among 63 patients with local treatment failures.

Progressive disease	Dead of cancer within 5 years	Dead of intercurrent disease within 5 years	Alive 2 years or more
Not radical	10/11	1/11	0/11
Doubtful radicality	4/4	0/4	0/4
Radical	6/6	0/6	0/6
Local recurrence			
Not radical	6/9	0/9	3/9
Doubtful radicality	6/9	1/9	2/9
Radical	6/24	3/24	15/24

CONCLUSIONS

Vulvectomy using warm knife- and open wound-technique is a simple and less traumatic procedure, and is suitable in most cases of malignant vulvar tumours. Local treatment failures were reported in 23 % of the patients which is consistent with the results obtained using radical vulvectomy and groin dissection in a one-phase procedure. Crude survival was 60 %, the complication rate was low and the hospitalization period short.

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Neoplasma 3/1983 (In press)

CO₂-LASER FOR THE TREATMENT OF INVASIVE VULVAR AND VAGINAL CANCER

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SUMMARY

In a material of 21 patients including seven primary and six recurrent vulvar carcinomas, five vaginal carcinomas, one urethral carcinoma and two preinvasive vulvar carcinomas operation was performed with a CO₂-laser scalpel. In nine radical and three partial vulvectomies no primary closing of the wounds was performed. In the remaining primary closing was performed.

The operative bleeding and healing process with laser scalpel and electro-surgical scalpel using open wound technique was about the same. The surgical time was longer with the laser technique but the operative specimens were better preserved. Healing of the primary closed wounds were uncomplicated.

INTRODUCTION

The first report of the laser surgery in gynecology was reported by Kaplan et al (9) who treated 11 patients with cervical erosions. That report has been followed by others (1, 4, 5, 8, 12, 13). The CO₂-laser has been applied in gynecologic surgery in the utilization of two different operating methods. One model is adjusted to the optical system of a colposcope, through which the laser beam can be used to destroy microscopic lesions with high precision. In the other model (Sharplan laser) the focused laser beam can be used as a thermal scalpel to perform surgical procedures.

Several centres have reported their experience of using laser in clinical surgery. In most reports the advantages of the laser beam are characterized as described by Joseph H Bellina (3): "As a surgical modality, the energy of the CO₂-laser, applied at appropriate power selections, permits the surgeon to separate tissues along a narrow line, as with a scalpel, or to vaporize large masses of tissue layer by layer, by judiciously playing the beam over the surface to be ablated. The depth of penetration and accuracy of tissue destruction are highly precise and visually controllable. Provided the diseased tissue is visible to the eye, either directly or through an operating microscope, it can be eradicated. No longer is the surgeon limited by confined spaces, in which the scalpel, cryoprobe or cautery cannot be manipulated effectively".

Numerous studies (1, 5, 13) indicate that the laser damage to residual tissue is indeed minimal, unlike that associated with cautery or cryosurgery, thus promoting rapid healing and reducing postoperative edema and scarring.

The aim of this investigation was to report our preliminary experiences with laser surgery in malignant vulvar and vaginal tumours.

MATERIAL AND METHODS

The instrument used was a Sharplan 733 CO₂-laser. The Sharplan 733 CO₂-laser has an articulated arm used to direct the CO₂-laser beam through an interior mirror system. The articulated arm can be covered with a sterile plastic sleeve and used in major surgery. This instrument's energy output can be changed from 1 to about 50 watts. A timer can deliver exposures from 1/20 of a second to 7 seconds, or the laser beam can be used continuously with a fast pedal control.

The material consists of 21 patients; seven primary and six recurrent vulvar carcinomas, two vaginal carcinomas, three vaginal metastases from carcinoma of the cervix uteri, one carcinoma of the urethral meatus and two pre-invasive vulvar carcinomas.

In all the operations we have used continuous beam of 20-30 watts output. In the patients with vaginal carcinomas or vaginal metastases we have done local radical resection of the tumour. In the patients with vulvar carcinoma vulva is removed with its underlying subcutaneous tissues and muscles.

The medial limit of the dissection is the hymenal ring, leaving the urethra. The lateral limit is the labio-crural fold crossing, the perineum above the anus caudally and mons veneris cranially with the intended minimum free margin to the tumour of 2 cm. Individualization of the resection line however, was sometimes necessary because of the localization and extent of the tumour. In the patients with preinvasive vulvar carcinomas we have done subcutaneous vulvectomy, only ½ cm of the subcutaneous tissue is removed.

In the patient with urethral cancer a resection of the distal third of the urethra was performed. On this patient we have performed groin dissection and the preparation of the skin flap was performed on one side with the laser, and on the other side with a sharp scalpel.

In all operations we have endeavoured to achieve macroscopic radical excision of the tumour tissue. In nine radical vulvectomies and three partial vulvectomies no primary closing of the wound has been performed. Following the successful excision of tumour tissue, the entire wound area was "coagulated"

using defocused laser beam. In the remaining cases, primary closing of the wound was performed.

RESULTS

All specimens have been defined by the pathologist as radical excisions. The examination of the specimens was uncomplicated due to the insignificant degree of tissue necrosis at the edges.

The surgical bleeding was of no consequence; in vulvectomies 25-800 ml, average 200 ml, in vaginal resections 25-200 ml, average 80 ml.

The surgical time consumed was relatively extended, in vulvectomies 50 min to 1 hour 45 min, average 1 hour 15 min, in vaginal resections 20 min to 50 min, average 40 min.

Complete healing of the wounds, in cases where primary closing was not performed, occurred 4-6 weeks after treatment. Maximal discomfort was reported approximately five days after laser therapy. In two cases, a short (5-10 days) postoperative infection was diagnosed. The infection was successfully treated by administration of antibiotics and was not seen to prolong the healing process. Where primary wound closing was performed the complete healing has been uncomplicated and the average time was 10 days. In other studies the skin healing is delayed in comparison to skin healing after surgery with sharp scalpel (7, 10, 14).

No significant difference in the healing pattern associated to laser surgery without primary closing as opposed to that of electrocautery has been registered.



Fig 1. Squamous cell carcinoma of the vulva.



Fig 2. The immediate result after laser resection with open wound technique.



Fig 3. Ten weeks after operation with open wound technique.

DISCUSSION

Several investigators have described that the CO₂-laser seals capillary vessels as it cuts (6, 10, 12). With normal flow in vessels, veins and arteries up to 0.5 mm in diameter are sealed by the laser beam. If the flow is reduced by administration of vasoconstrictor substance those up to 1.0 mm are sealed. Small bleeders can mostly be stopped by coagulation with the unfocused laser beam. The area to be coagulated, however, must be dry. If not, the covering blood absorbs the laser beam. Most bleeding vessels nevertheless, should be conventionally clamped with a hemostat and ligated. Hemostasis tended to improve with increased experience of the operator.

Our incisional technique employs an average of 25-30 watts output. Since the depth of the initial incision does not extend to more than 200 micron, repeat focused vaporization along the incisional line is necessary, therefore the surgical time is increased.

Our earlier experience of radical vulvectomies using electrosurgical scalpel shows that this does not entail significant increase of the surgical bleeding and the surgical time is reduced considerably compared to laser beam surgery.

The laser excised specimen is significantly better preserved than the specimen excised by use of electrocautery. But more experience is required in order to evaluate the possible advantages of laser surgery applied in radical vulvectomies. Controlled studies, evaluating bleeding, wound healing, operation time and radicality of excision are initiated.

Due to the high degree of precision and the accuracy with which malignant tissue, colposcopically recognized, may be ablated or destroyed, the laser beam technique may well be recommended for excision and/or vaporization of recurrent vulvar and vaginal carcinoma. The possibility of primary wound closing also reduces the time of wound healing.

Special indication for laser surgery in the vulva region is the vulvar carcinoma in situ. Since carcinoma in situ of the vulva occurs in a younger population conservative treatment is important and the CO₂-laser is an effective method of reliable conservative treatment (2, 11).



Fig 4. Cancer in situ of the vulva.



Fig 5. The immediate result after skinning laser resection of the vulva.

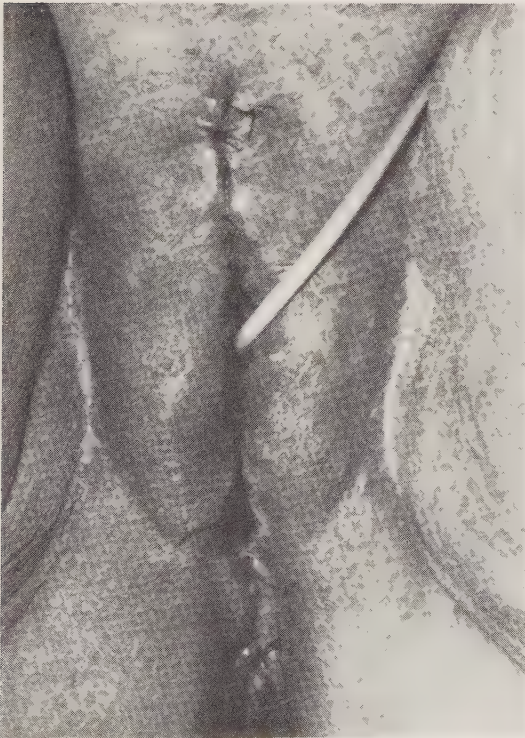


Fig 6. Primary closing of the wound.



Fig 7. Six weeks after primary closing of the wound.

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Acta Radiologica (Submitted for publication)

RADIOTHERAPY AND SURGERY IN THE TREATMENT OF REGIONAL LYMPH NODES IN SQUAMOUS CELL CARCINOMA OF THE VULVA

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SUMMARY

The material consisted of 244 patients with vulvar squamous cell carcinoma, of whom 114 were operated with groin dissection, which was complemented with pelvic lymphadenectomy in 24 cases. Positive lymph nodes were observed in 51 % of the patients. Preoperative radiation with a specification dose of 17.6 Gy (CRE = 11) was given. Specification doses of 10.1–35.5 Gy were given postoperatively if positive nodes were found (total CRE-values pre- and postoperatively = 11–15). Non-operated patients were given 17.6–42.8 Gy (CRE 11–16). Regional metastases after treatment occurred with negative nodes in 5 % of the patients, positive nodes in 42 % and in 20 % of those who received only radiation therapy. In cases of one-sided tumours, ipsilateral groin dissection is considered adequate if it is negative. In other cases, bilateral groin dissection should be done. Pelvic lymphadenectomy is not indicated when the groins are negative. In other cases, the indication is doubtful. The preoperative radiation therapy used in this material is considered adequate, but postoperative therapy should be administered with higher absorbed radiation doses.

INTRODUCTION

The regional lymph nodes are treated in most therapeutic schedules for malignant diseases. Taussig (1941) and Way (1951 och 1961) described the surgical measures to be taken for treatment of the regional lymph nodes in connection with vulvar cancer. Their technique is now considered classic and has become the usual measure at radical vulvectomy. Due to the relatively high morbidity and the amount of mortality seen at or following surgery, other methods of treating the regional lymph nodes have been suggested. Edsmyr (1962), Daly & Million (1974) and Wharton (1978) have used radiation therapy adjuvantly. Weghaupt (1978) and Kucera (1980) have also used this technique when inguinal metastases had been demonstrated.

This report accounts for the results of combined radiation therapy and surgery for treating the regional lymph nodes and seeks to establish the principles for their treatment in the future.

MATERIAL AND METHODS

The material consists of 244 patients with squamous cell carcinoma of the vulva treated at the Gynecologic Section of the Department of Oncology in the University Hospital of Lund, Sweden, between 1962 and 1979.

The staging according to the FIGO-system and classification of the regional lymph nodes in the different stages using the TNM-system (UICC) are shown in Table I. No suspicion of regional metastases existed in 160 patients (N_0 - N_1) (66 %), while 84 patients (34 %) had clinically demonstrated regional metastases or suspicion of such spreading (N_2 - N_3). Fine needle biopsy of the inguinal lymph nodes has as a rule not been done.

Table I. Classification according to FIGO and UICC.

FIGO	TNM			
	N_0	N_1	N_2	N_3
Stage I	72	7	-	-
Stage II	51	11	3	-
Stage III	15	3	46	-
Stage IV	-	1	8	27
Total	160 (66 %)		84 (34 %)	

Treatment of the primary tumour has consisted of radical vulvectomy with the warm knife- and open wound-technique. The regional lymph nodes have been operated on with groin dissection in 114 cases. Twenty-four of these patients have also had pelvic lymphadenectomy. The surgery has as a rule been carried out on two separate occasions, with groin dissection and lymphadenectomy six weeks after the vulvectomy. The surgical technique has been described in detail in earlier reports (Simonsen 1983, Simonsen et coll 1983).

The radiological treatment of the regional lymph nodes has been done both preoperatively and postoperatively; some patients received only radiation therapy (Table II).

Table II. Radiological treatment of the inguinal regions in 244 patients with vulvar carcinoma.

Treatment	Primary target	Primary and secondary target	Total
Solely pre-operative	71	-	71
Preoperative + postoperative	17	23	40
Solely post-operative	1	2	3
Only radiation therapy	85	12	97
Not treated	-	-	33
Total	174	37	244

1. Preoperative radiological treatment.

Radiation therapy was given preoperatively in connection with vulvectomy. The target includes the inguinal lymph node stations. The deepest part of these was assumed to be located 3 cm below the skin surface. A ^{137}Cs -unit was used with a single-field technique, a field size of 8 x 13 cm and SSD of 20 cm. The peak absorbed dose was 7 Gy per fraction with three fractions a week and a total of 21 Gy. This gives a specification dose of 17.6 Gy in the specification point being defined on the central axis of the field at the centre of the target volume i.e. at 1.5 cm depth. The dose variation in the target then will be from 15 to 21 Gy. Of the 114 patients given groin dissection, 111 also received preoperative radiation therapy.

2. Postoperative radiation therapy.

Patients in whom malignancy was demonstrated in the surgical specimens have as a rule received complementary radiation therapy in one or both sides. The primary target included the operation area, which was defined in the same way as the inguinal lymph node stations. Eighteen patients (42 %) (including one patient not given preoperative treatment) out of a total of 43, were given postoperative radiotherapy to the primary target alone.

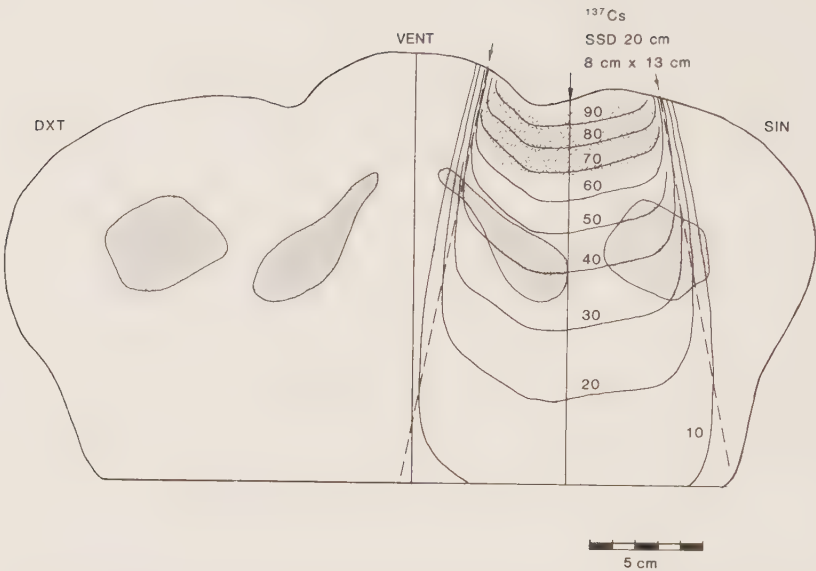


Fig 1. Treatment planning of the inguinal lymph nodes (primary target) using single beam therapy (^{137}Cs).

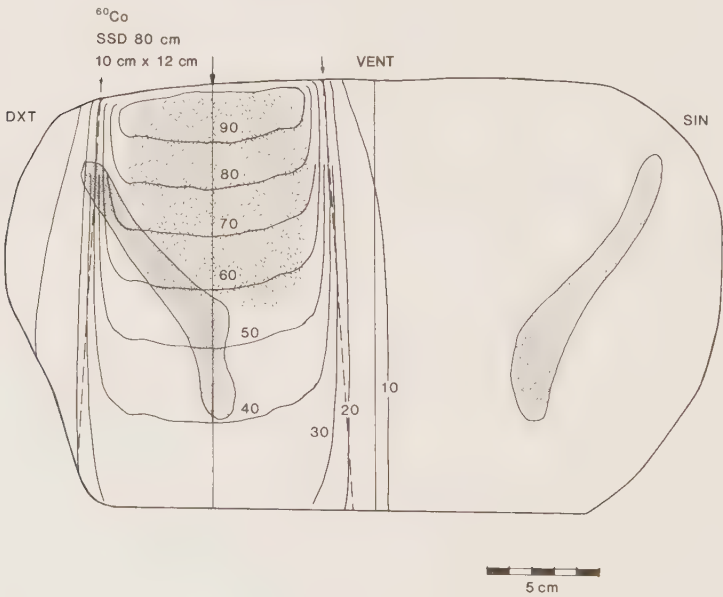


Fig 2. Treatment planning of inguinal, external iliac and interiliac lymph nodes (primary and secondary target) using single beam therapy (^{60}Co).

During recent years, treatment of a secondary target has increased. This consists of the external and interiliacal lymph node stations in the pelvis. The deepest part of these was assumed to be located 10 cm below the surface of the skin. The specification point of the secondary target volume is defined as the centre of the target i.e. at 5 cm depth. The absorbed dose of the total target volume, including both primary and secondary target, has been specified at the centre point of the total target i.e. at 5 cm depth. Twenty-five (58 %) out of 43 patients, including two not given preoperative radiation therapy, were given postoperative radiation therapy both to primary and secondary target.

When only the primary target was treated postoperatively, a ^{137}Cs -unit was used, with the same SSD and field size as described for the preoperative treatment. The peak absorbed dose was 3 Gy per fraction, five fractions a week and the specification dose varied from 10.1 Gy to 35.5 Gy, with a variation within the target of 8.5-12 Gy to 30-42 Gy, respectively.

The postoperative treatment started during the first ten days postoperatively, and as a rule a specification dose of 10.1 Gy (4 fractions) was given. After three-to-five weeks, the remaining irradiation was delivered.

When both targets were treated postoperatively, a ^{60}Co -unit and single-field technique was used with SSD 80 cm and a field size of about 150 cm². The peak absorbed dose was 3 Gy per fraction, five fractions a week. The specification dose varied from 9.6 Gy to 33.6 Gy with a variation within the target from 6.8-12 Gy to 24-42 Gy, respectively.

The postoperative treatment started during the first ten days postoperatively, and as a rule, a specification dose of about 9.6 Gy (4 fractions) was given, using bolus over the wound area to compensate for the build up effect. After three-to-five weeks, the remaining irradiation was given. In three patients, two medially angled fields with wedge filters were used, with a target absorbed dose for both the primary and secondary target of $(20.4 \pm 10 \%)$ Gy, $(37 \pm 11 \%)$ Gy and $(39 \pm 5 \%)$ Gy, respectively. This technique is described in the next section.

3. Radiation therapy alone.

Patients who were judged as being too frail for lymph node evacuation, or who refused to submit to surgery, were given radiotherapy alone. There were 97 such patients, of whom only the primary target in 85 were treated. The

technique and fractionation were the same as that described for the preoperative treatment. A specification dose varying from 17.6 Gy to 23.5 Gy was given in the first series in connection with vulvectomy. Fifty-one patients received no further treatment. The other 34 patients were treated on a second series about three weeks later, with a peak absorbed dose of 3 Gy per fraction, five fractions a week. The total specification dose varied from 27.7 Gy to 42.8 Gy.

Both targets were treated in 12 patients. A ^{60}Co -unit and single-field technique were used. SSD was 80 cm, and field size was about 150 cm². The peak absorbed dose was 3 Gy per fraction, with five fractions a week. The specification dose for secondary target has varied from 28.8 Gy to 41.6 Gy. As a rule, the treatment was given in two series, three weeks apart, with 16 Gy to 24 Gy in the first series.

Four patients were treated with two different treatment techniques both using a ^{60}Co -unit with 80 cm SSD. Both targets were treated. A multi-section dose plan was done to each patient using X-ray localization films to establish the target volumes. A: Two opposed antero-posterior fields with a field size of about 6-10 x 12 cm. The peak absorbed dose was 3 Gy per fraction, five fractions a week. Each field was treated daily. The caudal part of the posterior field (up to the cranial part of the symphysis) was given reduced irradiation with a field-weight of 0-75 %, depending on the anatomic situations. The treatment was given in two series three weeks apart. The absorbed dose to the total target was $(31.4 \pm 10 \%)$ Gy in the first series. One patient was given only the first series. Two patients were given two series with a total absorbed dose to the total target of $(58.8 \pm 10 \%)$ Gy and $(62.0 \pm 5 \%)$ Gy, respectively. B: Two anterior medially angled fields with wedge filters were used, field size about 8-13 x 12 cm. The peak absorbed dose was 3 Gy per fraction, five fractions a week. Both fields were treated daily. One patient has been treated with this technique. The target absorbed dose for the total target was $(32.5 \pm 5 \%)$ Gy.

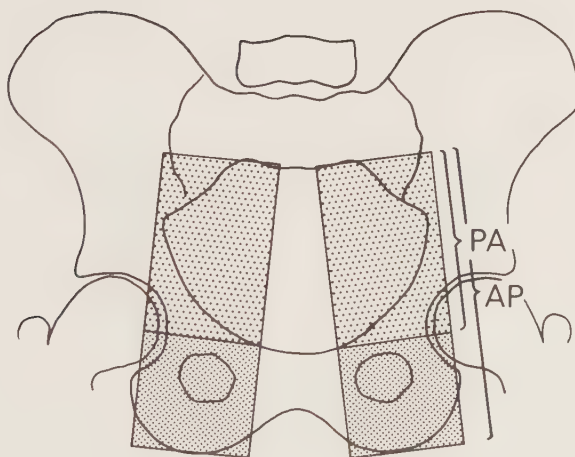
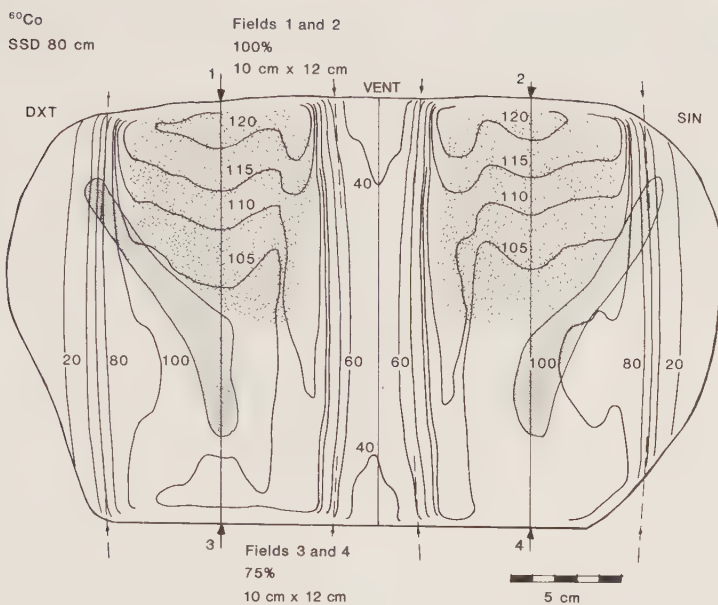


Fig 3 a. Treatment planning of inguinal, external iliac and interiliac lymph nodes (primary and secondary target) using two opposed weighted beams.

b. The caudal part of the posterior field has a different weight.

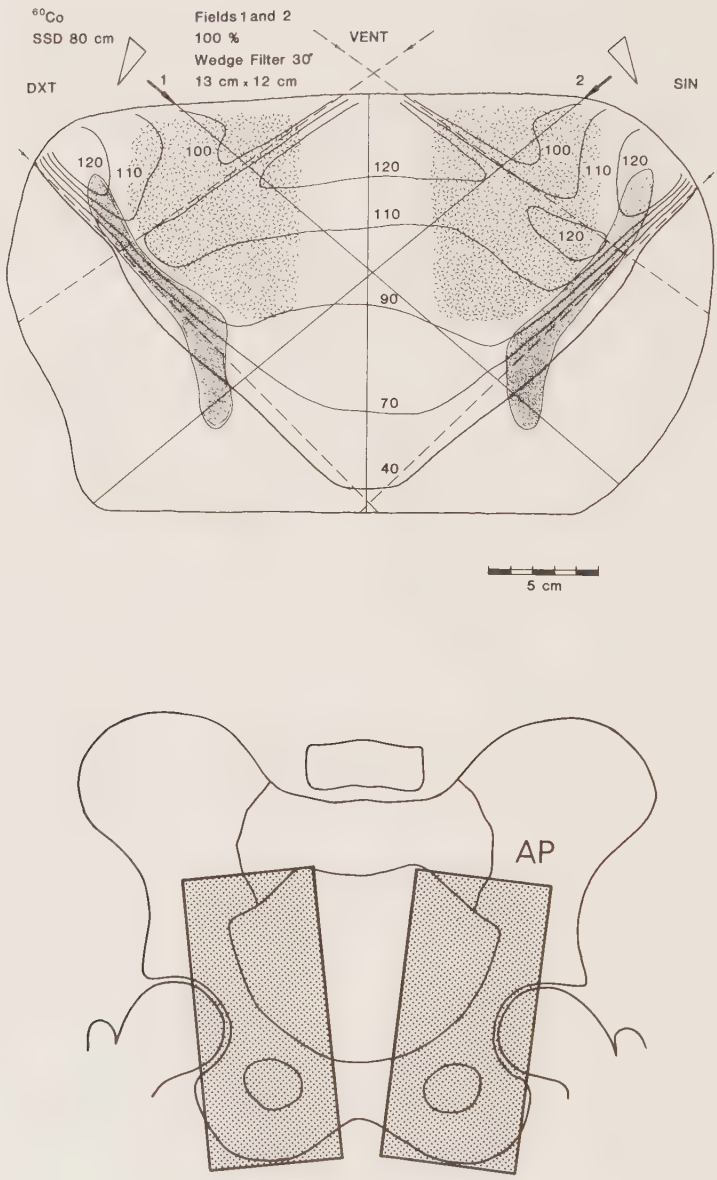


Fig 4a-b. Treatment planning of inguinal, external iliac and interiliac lymph nodes (primary and secondary target) using two medially angled fields with wedge filters.

Thirty-three patients received no treatment of the inguinal lymph nodes. This depended as a rule on the small tumour size with little risk for spreading to the regional lymph node stations.

The radiological technique used has varied in respect to the photon energies delivered, and the pattern of fractionation employed. CRE-calculations according to Kirk et coll (1971) were done in an attempt to evaluate the biological effectiveness of the variations used. Table III shows the CRE-values for the patients in the different treatment groups.

Table III. CRE-values for the treatment of inguinal and pelvic lymph node stations in 111 patients.

Treatment	No. of patients	CRE	
		Primary target Inguinal lymph nodes	Secondary target Pelvic lymph nodes
Preoperative irradiation only	71	11	
Pre- and post- operative irradiation	17	11 - 12	
	18	12 - 13	9 - 10
	3	15	11 - 12
	2	17	14
Irradiation only	51	11	
	12	12 - 14	
	22	15 - 16	
	5		11 - 12
	7		>12 - 14

The findings at lymph node evacuation are accounted for in relation to the preoperative status of the nodes. The regional metastases are recorded if they have constituted the only treatment failure in the patient or if they have occurred together with local recurrences. They are reported in relation to the preoperative lymph node status, in relation to the type of treatment and the surgical findings, and in relation to the radiation therapy given.

Complications in the form of leg oedema that required treatment with diuretica and bandage, and thromboses during and following treatment are reported.

These conditions have not been recorded when they occurred in connection with metastases. The patients have been observed for periods varying from 2-17 years.

RESULTS

No clinical suspicion of regional metastases existed for 160 patients (N_0 - N_1). Seventy of these had groin dissection, of whom eight were also submitted to pelvic lymphadenectomy. Table IV shows the histopathological findings at surgery. Metastases in the regional lymph nodes were found in 24 of 70 patients (34 %) which had not been found at clinical examination.

Suspicion of, or clinically demonstrated, metastases were recorded in 84 patients (N_2 - N_3), of whom 44 were operated with groin dissection. Sixteen of these patients also had pelvic lymphadenectomy. Table IV shows the histopathological findings at surgery. In 10 out of 44 patients (22 %) no metastases in the regional lymph nodes were found, though there had been suspicion of this at clinical examination. The metastases in the lymph nodes found after completion of treatment are accounted for in Table V, according to treatment group (Tables IV and V).

Table VI shows the radiological treatment, expressed in CRE-values, which was given the different groups who had lymphadenectomy. The regional treatment failures observed are also tabulated. Higher radiation doses were given those patients with perinodular growth, especially when surgery had not been macroscopically radical. The secondary target has also been treated when tumour growth has been extensive (Table VI).

The different treatment groups are not strictly comparable, and it was not possible to evaluate the effectivity of the different radiation doses.

The CRE-values in cases where only radiation treatment of the regional lymph nodes was given and the regional treatment failures recorded are shown in Table VII. This group also received treatment of the secondary target and higher radiation doses were given when there was an increasing tumour engagement of the regional lymph nodes. No evaluation of the effectiveness of the radiation doses could be made in this group, either (Table VII).

Table IV. Results of histopathologic analysis following lymphadenectomy in 114 patients.

TNM	No. of patients	No cancer	Groin dissection Cancer in lymph nodes	Cancer out-side lymph nodes	No. of patients	No cancer	Pelvic dissection Cancer in lymph nodes	Cancer out-side lymph nodes
N ₀ -N ₁	70	46	10	14	8	6	-	2
N ₂ -N ₃	44	10	9	25	16	7	1	8

Table V. Number of metastases after conclusion of treatment among 114 patients.

TNM	Total no. of metastases	Total no. of patients	No treatment	Irradiation only	Irradiation and lymphadenectomy
N ₀ -N ₁	20/160 (13 %)		2/25	11/65	7/70
N ₂ -N ₃	30/84 (36 %)		2/8	8/32	20/44

Table VI. Results of histopathologic analysis, number of regional treatment failures and CRE-values in 111 patients given pre- and postoperative irradiation.

Treatment	No. of patients	CRE in		No. of metastases/No. of patients		
		primary target	secondary target	No cancer	Cancer in lymph nodes	Cancer outside lymph nodes
Preoperative irradiation	71	11		3/56	2/7	3/8
Pre- and postoperative irradiation	17	11			0/4	5/13
	18	12 - 13	9 - 10		2/7	8/11
	3	14 - 15	11 - 12		1/1	2/2
	2	17	14		0/0	0/2
Total				3/56	5/19	18/36

Table VII. Regional treatment failures in CRE-values for patients who received only radiation therapy.

Primary target	CRE in		No. of metastases/ No. of patients
	Secondary target		
11			7/51
12 - 14			3/12
15 - 16			5/22
	11 - 12		2/5
	>12 - 14		2/7
Total			19/97 (20 %)

Regional treatment failures were found in 3 of the 56 patients in whom no tumour could be demonstrated in the excised lymph nodes; 5 of 19 patients with tumour in the lymph nodes had regional treatment failures and so many as 18 of 36 patients with perinodular growth (Table VI).

Table VIII shows the histopathological findings in the inguinal and pelvic lymph nodes at lymphadenectomy in the pelvis and the regional treatment failures.

Table VIII. Results of histopathologic analysis following pelvic lymphadenectomy in 111 patients given preoperative radiation therapy.

No. of patients	Groin dissection			Pelvic lymphadenectomy		
	No cancer	Cancer in lymph nodes	Cancer out-side lymph nodes	No cancer	Cancer in lymph nodes	Cancer out-side lymph nodes
2	2	-	-	2	-	-
6	-	6	-	6	-	-
1*	-	1	-	-	1	-
5**	-	-	5	5	-	-
10***	-	-	10	-	-	10
24	2	7	15	13	1	10

* 1 regional treatment failure(s)

** 1 " " "

*** 5 " " "

Of the 24 patients in whom pelvic lymphadenectomy was performed, regional treatment failures were recorded in 7 cases. These were in all seven cases localized in both the inguinal and pelvic sites of surgery.

Nineteen of the 87 patients who underwent groin dissection got regional metastases. In fifteen of these, the metastasizing was judged as occurring in the pelvic site of surgery (4 cases) or in both the pelvic and the inguinal site of surgery. Only four of these patients had metastases limited to the inguinal site of surgery. Nineteen of the 97 patients (20 %) who were only given radiation therapy of the regional lymph nodes later had regional metastases. Ten cases were adjudged as being in the pelvic lymph nodes or in both the inguinal and pelvic lymph nodes.

No case of leg oedema or thrombosis was recorded among the patients who only received radiological treatment of the inguinal and pelvic regions. Leg oedema was recorded in 5 of the 24 patients (about 21 %) in whom pelvic lymphadenectomy was performed. The corresponding number for the group given groin dissection alone was 12 out of 90 patients (13 %). Thrombosis was observed in 7 of 114 patients (6 %), of whom three also showed symptoms of pulmonary embolism. Infected sores requiring treatment with antibiotic drugs were recorded in 12 of 114 patients (11 %). No skin necrosis was seen, and there was no per- or postoperative mortality.

DISCUSSION

It is extremely difficult to clinically evaluate tumour growth in inguinal lymph nodes. Most reports in the literature give figures of 16-39 % metastases found at groin dissection in patients who were thought to have normal or benignly affected lymph nodes (N_0 - N_1) (Way 1960, Lundwall 1961, Plentl & Friedman 1971, Daly & Million 1974). This agrees quite well with the rate for the present material, which was 34 %.

It is also difficult to judge the abnormal inguinal lymph nodes. Twenty-two per cent of the patients who were thought to have clinically obvious metastases or where this was suspected (N_2 - N_3) had no evidence of metastases at lymphadenectomy. Other centres have reported similar experience (Way 1960, Lundwall 1961, Edsmyr 1962, Plentl & Friedman 1971).

It can still be asserted that the clinical evaluation of the inguinal lymph nodes generally gives a good picture of the tumour growth in the nodes. This is also supported by the fact that regional treatment failures were observed in 10 % of the patients who received lymphadenectomy in the N_0 - N_1 -group, while 45 % of the N_2 - N_3 -group had regional treatment failures. It is, however, probable that greater certainty can be attained in the preoperative evaluation of the patient if fine needle biopsies are performed as clinical routine.

Lymphadenectomy on both sides has been recommended during the last decades due to the risk for metastasizing to the contralateral side when the vulvar tumour is one-sided (Plentl & Friedman 1971, Way 1982). No solely contralateral metastases have been observed in this material and no increase in frequency of metastases to the pelvic nodes has been observed in tumours of the clitoral region. One-sided tumours which are not near the midline ought to be satisfactorily treated with ipsilateral inguinal lymphadenectomy. If metastases are found, then operation ought to be performed on the contralateral inguinal region. There has been some discussion as to whether or not pelvic lymphadenectomy ought to be performed in connection with inguinal lymphadenectomy, and, if so, in what situations this is warranted. Some authors are of the opinion that pelvic lymphadenectomy ought to be done as routine at lymph node evacuation (Way 1948, Rutledge et coll 1977). Others perform a histopathological examination of the excised nodes at surgery. If the inguinal nodes are judged as positive, the operation is carried on with pelvic lymphadenectomy. If they are negative, the operation is finished without such measures (Way 1957). It is very seldom that one finds metastases in

the pelvic nodes, but not in the inguinal nodes, thus pelvic lymphadenectomy is not motivated when the inguinal nodes are normal (Morley 1976, Andreasson 1980, Iversen 1981).

Half of the patients who received lymphadenectomy had no tumour in the excised lymph nodes. Five per cent of these got regional metastases during the observation period. Lundwall (1961) and Edsmyr (1962) have reported similar figures. It is not possible to ascertain if this is due to an inadequate technique for the lymphadenectomy, or if the tumour was not discovered at the routine histopathological evaluation (Lundwall 1961).

The patients in whom tumour was demonstrated in the excised nodes had a higher frequency of regional treatment failures. This was mostly seen in cases where tumour growth was demonstrated outside the capsule of the node (about 50 %). There are not many reports in the literature on regional treatment failures after treatment of the lymph node stations. Lundwall (1961) has, however, reported the same frequency of metastases in a material of 39 patients; local recurrences were, however, also included.

The surgical findings and frequencies of metastases discussed above include the 24 patients who received pelvic lymphadenectomy. No tumour growth was observed in the pelvic lymph nodes in any of these patients except there was also tumour in the inguinal lymph nodes.

Pelvic lymphadenectomy has as a rule not been performed in this material, except in those cases where clinically suspected or verified metastases have been found in the inguinal regions. This explains the relatively high frequency of metastases (11/22). Plentl & Friedman (1971) stated that "about one-third of patients with any positive nodes have pelvic nodes involvement".

Regional treatment failures occurred in five of the ten patients who had perinodular growth in the excised pelvic nodes. This is a rather low frequency. It is not possible to judge the effects of radiation therapy in this connection. It can be difficult to clinically investigate the localization of regional treatment failures in the inguinal or pelvic regions. All of the metastases in the patients who received pelvic lymphadenectomy were recorded in both the inguinal and pelvic areas.

Metastases in the pelvic region also dominated in those patients who only had groin dissection, while about half of the patients who had received radi-

ation therapy of the regional lymph node stations developed pelvic metastases.

Radiation therapy has, with only a few exceptions, been given preoperatively in connection with lymphadenectomy. Postoperative treatment has, as a rule, been given only if tumour was demonstrated in lymph nodes or if non-resectable metastasizing to the lymph nodes was found. There has been much discussion as to whether radiation therapy should be given pre- or postoperatively (Perez 1970, Hamberger & Wharton 1978). The advantages of preoperative therapy have been considered to support this approach. Most of the patients are of advanced age, and it can be seen at vulvectomy, which is rather well-tolerated by these patients, if lymphadenectomy can be carried out as planned. If this is not judged as being advisable, the preoperative radiation therapy can be the first series of irradiation, which is the sole treatment of the regional lymph nodes.

The photon energy used (gamma-radiation from a ^{137}Cs -unit) has, with single-field technique, a variation of the absorbed dose in the primary target in relation to the specification dose of $\pm 17\%$, which is acceptable. Gamma-radiation from a ^{60}Co -unit with single-field technique has, as a rule, been used when there has also been a secondary target (external and interiliac lymph nodes). This technique gives only negligible variations of the absorbed radiation dose in the primary target, but in the secondary target the variation is $\pm 27\%$ in relation to the specification dose, which is not satisfactory.

In order to get a more even distribution of the absorbed radiation dose in the target, two different techniques have been used in a small number of patients. Both of these techniques have utilized a ^{60}Co -unit. One of them has two medially angled fields with a wedge-filter. This method gave a satisfactory distribution of dose in the target, with a variation of $\pm (5\% - 11\%)$. It was, however, not satisfactory in that the patient received rather high radiation doses in relatively large areas of non-tumourous tissue; hot spots occurred laterally in subcutaneous tissue in some patients. This in turn caused poor healing after lymphadenectomy, pronounced subcutaneous fibrosis and repeated small ulcerations in the inguinal skin during the follow-up period in one patient, who had received a total specification dose of 50.1 Gy in the primary target.

The other technique used two opposing fields. This technique gave satisfactory dose distribution in the target, with a variation of $\pm (5\% - 10\%)$, and

low radiation doses to surrounding tissues. This technique agreed quite well with that described by Daly & Million (1974) and Hamberger & Wharton (1978), and ought to be the method most suitable at present for the radiological treatment of inguinal and pelvic lymph node stations postoperatively, or when irradiation constitutes the sole treatment given.

The radiation therapy techniques used have not only varied in respect to the photon energies employed, but have also had different fractionation patterns. This makes it difficult to evaluate and compare their effects on the tumour, and for this reason their biological effectiveness has been calculated according to the method of Kirk et coll (1971). The CRE-value thus obtained is a measure of the biological effect on normal connective tissue. Most radiation therapy centres consider the CRE-value for normal connective tissue tolerance to be about 19.0. Even though the CRE-value does not give any measure of the effect on tumour, it is a useful instrument for comparing different patterns of fractionation and for working out radiation therapy techniques.

The preoperative radiation dose used is about the same as that used by clinic for the preoperative irradiation of the contents of the true pelvis; it is rather low, considering the treatment volume, which contains no critical organs. Schultze et coll (1980) used a "tumour dose" of 45 Gy and Hamberger & Wharton (1978) used 45-50 Gy for treating the inguinal and external iliac areas, with a fractionation of 2 Gy per day, five fractions a week, which corresponds to a CRE-value of 14-16. Acosta et coll (1978) used 50-55 Gy from a ^{60}Co -unit and single-field technique with the same fractionation scheme as that described above. Jafari & Magalotti (1981) used 30-60 Gy preoperatively to the inguinal regions in cases of stage III and IV- tumours.

The postoperative radiation doses in patients with positive lymph nodes have been unsatisfactorily low. Hamberger & Wharton (1978) stage that "A minimum of 50 Gy tumour dose" to all areas, using the previously described fractionation, is desirable for positive lymph nodes following primary lymphadenectomy. Weghaupt (1978) used 50-60 Gy in the same situation, but a tumour dose of 45 Gy was reported by Schultze et coll (1980).

The radiation doses administered have also been low when only radiation therapy has been used for treating the regional lymph node stations. Daly & Million (1974) recommended a "tumour dose" of 45 Gy in fractions of 2 Gy per day as adjuvant treatment of clinically normal inguinal regions. If this is

given with five fractions a week, it corresponds to a CRE-value of 14. No regional treatment failures were recorded in six patients with observation periods of 6-36 months.

Frankendahl (1977) used 30-60 Gy with the same fractionation as described above. Both Weghaupt (1978) and Kucera (1980) used a tumour dose of 60 Gy for irradiation of metastases in regional lymph nodes or when there was suspicion of metastases.

In this material, higher doses of irradiation have been administered when tumour growth was more advanced in the regional lymph nodes. The recorded frequencies of regional treatment failures thus mainly reflect the status of the tumour in the regional lymph nodes. It is not possible to definitely judge the effect of irradiation on the tumour.

Combined surgical and radiological treatment of the regional lymph nodes has not resulted in any high frequency of complications: infections were found in 11 % of the patients, thrombosis in 6 %, and no case of skin necrosis. The main reason for this is probably that evacuation of the lymph nodes has been done on a second occasion, using separate incisions. Large surgical wounds, which must be covered with the surrounding skin or transplanted skin and plastic surgery are thus avoided in most cases (Hamberger & Wharton 1978, Hacker et coll 1981). As the medial-caudal part of the surgical wound is left open, the problem with lymph drainage is usually eliminated.

The frequency of moderate-to-severe permanent leg oedema requiring treatment with diuretica and/or bandage was 13 % in those patients who had groin dissection and about 21 % in those given pelvic lymphadenectomy, which agrees quite well with the reports of Lundwall (1961), Rutledge et coll (1970) and Hacker et coll (1981), even if higher frequencies have been reported elsewhere. Calame (1980) reported 65 % leg oedema in a material of 58 patients in whom pelvic lymphadenectomy had been done. It is difficult to judge the contribution of radiation therapy to the occurrence of leg oedema. No such complaints have been recorded when radiation therapy has been the sole treatment given. The radiation doses used at operation have been low or relatively low. The oedema recorded is probably mostly due to the effects of surgery, which is also asserted by Edsmyr (1961) and Acosta et coll (1978).

Due to the often high rates of morbidity at radical vulvectomy combined with lymphadenectomy, especially when pelvic lymphadenectomy is performed, differ-

ent attempts have been made to modify the treatment technique. Hacker et coll (1981) described a surgical technique especially suitable for patients without any clinical suspicion of regional metastases, where vulvectomy and lymph node evacuation were performed with separate incisions. Serious complications were observed in 21 % of the patients given such surgery, and of these there was major break down of the groin incision in 14 cases. The same number of leg oedema was found. There was less morbidity using this technique, and the survival rate was not compromised, either. Another way is to replace the adjuvant inguinal lymphadenectomy with radiation therapy, which has been proposed by different authors (Daly & Million 1974, Frankendahl et coll 1977, Hamberger & Wharton 1978, Weghaupt 1978, Schultz et coll 1980). Reports on the use of this method in cases of squamous cell carcinoma in other parts of the body have been published (Whithers & Peters 1978). Frankendahl et coll (1977) reported no regional treatment failures in 12 patients treated for squamous cell carcinoma in the vulva after 30-60 Gy radiation dose to the inguinal regional lymph nodes. Three regional metastases occurred in 17 patients not given radiation therapy. Schultz et coll (1980) reported one case of regional metastasis in 38 patients treated prophylactically with an absorbed radiation dose of about 60 Gy in the inguinal regions, and five metastases in 35 patients not given prophylactic treatment.

Most therapists prefer lymphadenectomy instead of radiation therapy when curative therapy is sought for suspected or demonstrated metastases in the regional lymph nodes, if the age and general condition of the patient allow such a measure (Hamberger & Wharton 1978). This is supported by the radiobiological conditions concerning the radiosensitivity of the often hypoxic central areas of palpable tumours.

Weghaupt (1979) and Kucera (1980) used 50-60 Gy in the inguinal regions, however, even in these situations, and operated only when the metastases did not respond to radiation therapy.

CONCLUSIONS

Ipsilateral inguinal lymphadenectomy appears to be adequate for treating one-sided vulvar tumours where metastases in the inguinal regions are not suspected (N_0-N_1), if no metastatic growth has been found at histopathologic analysis of excised lymph nodes. If tumour is demonstrated, the operation should be carried out with lymphadenectomy even on the contralateral side of the inguinal region. If metastases in the inguinal region have been found or are suspected

(N₂-N₃), bilateral inguinal lymphadenectomy ought to be done. In midline tumours, bilateral inguinal lymphadenectomy ought to be done irregardless of the lymph node status.

Pelvic lymphadenectomy is not indicated when the inguinal lymph nodes are free of tumour. The value of pelvic lymphadenectomy is doubtful, even in cases of positive inguinal lymph nodes. Pelvic metastases indicate such wide spreading of the tumour disease that it is probably generalized, so that non-surgical therapy with less morbidity would appear preferable.

Postoperative radiation therapy of the inguinal lymph node stations with the absorbed target dose described here appears to be adequate.

Postoperative radiation therapy in patients with positive inguinal lymph nodes ought to cover the inguinal, external and interiliac lymph node stations on both sides, and be administered with higher absorbed target dose than has been done in this material.

Adjuvant radiation therapy in patients not submitted to lymphadenectomy ought to be given using higher absorbed target doses than those used in this material. Patients having suspected or demonstrated metastases in the inguinal regions (N₂-N₃) who are not given lymphadenectomy ought to receive irradiation of the inguinal, external and interiliac lymph nodes, using an absorbed target dose close to that tolerated by normal connective tissue.

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BLEOMYCIN ALONE OR COMBINED WITH MITOMYCIN C
IN TREATMENT OF ADVANCED OR
RECURRENT SQUAMOUS CELL CARCINOMA OF THE VULVA

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SUMMARY

Twenty patients with advanced and/or recurrent vulvar carcinoma were treated with bleomycin alone or combined with mitomycin C. Five of 11 patients in the bleomycin-treated group showed objective response (two complete and three partial) and five of nine patients in the bleomycin-mitomycin C-treated group showed objective response (one complete and four partial). No severe side effects were seen. Now that activity against this disease has been demonstrated for bleomycin, alone or combined with mitomycin C, attention should be directed to treating those patients not cured by surgery and radiation therapy alone.

INTRODUCTION

Cancer of the vulva is a rare disease, constituting only 3 %-4 % of all gynecologic malignancies. It is a disease of old age with an average accession incidence maximum at the age of 65. The treatment of choice is radical vulvectomy with dissection of the inguinal and femoral lymph nodes, as well as external and internal iliac lymph nodes in selected cases. In our clinic this radical surgery is combined with preoperative radiotherapy to the inguinal nodes, and in large lesions to the vulva region. The results of this therapy model are good. The 5-year tumour death rate for all stages is about 35 %.

Because of the good primary treatment results, recurrent carcinoma of the vulva is an uncommon disease. Patients with this disease are also likely to be older and thus subject to physiologic impairments which often contraindicate chemotherapy. Therefore, the number of published systemic evaluations of different chemotherapy schedules is small and includes only small numbers of patients.

There are some data on the use of doxorubicin (Adriamycin) (1-3), bleomycin (1, 3, 5-15), cyclophosphamide (16, 17), cytembena (18), 5-fluorouracil (19), 6-mercaptopurine (19), methotrexate (19-22), mitomycin C (19), nitrosoureas (23), and porfiromycin (24); for review, see Deppe et al (25). It is only doxorubicin, bleomycin and cytembena which allow any conclusion considering the responses: four of six, 28 of 44, and four of 26 patients, respectively.

Thus far there are only eight reports on the use of combination chemotherapy (16, 25-30). Turner's* combination regimen, bleomycin, vincristine, and

*Turner R. Paper read at the Bleomycin Meeting, Hammersmith Hospital, London, England, Oct 1975

methotrexate, proved highly effective in advanced patients; however, it produced toxic effects in some of these patients. Of seven patients in Turner's series, two died within 1 month of treatment, and only one of the remaining five did not respond to treatment. We report here on two regimens, bleomycin alone and bleomycin combined with mitomycin C in primarily advanced or recurrent squamous cell carcinoma of the vulva.

MATERIAL AND METHODS

Two patients with primarily advanced cancer of the vulva and 18 with recurrent and/or distant metastatic cancer of the vulva were selected on the basis of the following criteria: evaluable lesions; disease not previously treated by surgery and/or radiotherapy; leukocytes $\geq 3,0 \times 10^9$ /liter and platelets $> 100 \times 10^9$ /liter; and Karnofsky performance index ≥ 50 . All the 20 patients had squamous cell carcinoma. Eighteen of the patients had previously received external-beam radiotherapy and had had a radical vulvectomy. Two patients had such advanced disease that chemotherapy was used as the primary treatment regimen.

The bleomycin regimen used was 15 mg im twice a week up to a total dose of ≤ 300 mg. The combination bleomycin-mitomycin C regimen used was: bleomycin, 5 mg iv during 6-8 hours on Days 1-7; and mitomycin C, 10 mg iv on Day 8 as a bolus dose. This dose schedule was given as one course repeated four times with a 1-week recession period between each course.

Initial examination included physical examination, cbc, ECG, lung roentgenogram, and gynecologic palpation. When indicated, by symptoms or known metastases, skeletal surveys and isotope scans of the liver, brain, and skeleton were performed.

The criteria for response was defined as follows: complete remission (CR) - total disappearance of all measurable lesions for at least 1 month; partial remission (PR) - at least 50 % reduction of measurable tumour, static disease (SD) - 0-49 % decrease of measurable tumour volume and no new lesions; and progressive disease (PD) - increasing volume of tumour or new lesions during treatment.

RESULTS

Five of 11 patients in the bleomycin-treated group showed objective response (two CRs and three PRs). The two patients with CR responded for 4 and 24+ months, respectively, and the three patients with PR responded for 2, 2 and 3 months. Median survival for responders was 13 months compared to 3 months for nonresponders. Three of the responders had a recurrence and the other two had distant metastases (Table I).

Five of nine patients in the bleomycin-mitomycin C-treated group showed objective response (one CR and four PRs). Two patients had SD. The patient with CR is still responding after 7 months. Three of the four patients with PRs are still responding after 2+, 3+, and 7+ months. Two of the responders received bleomycin-mitomycin C as the primary treatment. Two of the responders had recurrence of primary tumour and one patient had recurrence in distant metastases (Table I).

Toxicity

In the bleomycin-treated group one patient developed fibrosis of the lung, two developed urticaria, and three developed fever which responded well to symptomatic treatment. In the bleomycin-mitomycin C group three patients developed fever (during the bleomycin treatment), one developed reversible pneumonitis, and four developed moderate thrombocytopenia. No lethal side effects were seen.

DISCUSSION

It is not possible to cure a patient with vulvar carcinoma with chemotherapy administered in a recurrent or metastatic situation. Thus, chemotherapy in situations like this is a palliative treatment, and pronounced side effects can certainly not be accepted, since the patients often are old and subject to physiologic impairments.

Deppe et al (25) reported a promising regimen in four patients treated with doxorubicin. Three of their four patients obtained regression for 28+, 31+, and 32 months without complications. Guthrie (31) and the present authors have also treated patients with vulvar cancer with doxorubicin in conventional doses but with severe toxicity and without any success. Edsmyr (13) reported a >50 % tumour reduction in two of three patients with advanced vulvar cancer using bleomycin with only moderate side effects.

Encouraged by the Edsmyr's results and the unsatisfactory results obtained previously in our clinic in recurrent vulvar cancer, we decided to try bleomycin as a single drug in treating these patients. Five of 11 of our patients responded and the incidence of toxicity was low. The prolongation of life in the responders was significant compared with the nonresponders.

Miyamoto et al (32) renewed the interest for chemotherapy with combination bleomycin and mitomycin C therapy for advanced squamous cell carcinoma of the cervix. We started their regimen in advanced and recurrent cervical cancer and obtained good results and almost no side effects. Considering these promising results we decided to undertake a phase II trial of advanced and/or recurrent vulvar carcinoma trying to improve our bleomycin results. Though it is too early to state anything definitive about the duration of remission and survival or to compare the data with bleomycin alone or other regimens, the response rate of five of nine patients is promising. The palliative effect of the bleomycin-mitomycin C regimen was good and most of the patients led an almost normal life. In contrast to patients with cervical cancer, responses were observed both in sites of local recurrence and in distant metastases; responses in patients with cervical cancer have usually been limited to responses in distant and metastatic sites.

Now that activity against this disease has been demonstrated for different cytostatic drugs, it should be possible by careful consideration to combine the various modalities of treatment, thereby providing a hope of longer survival and, ideally, a higher cure rate.

Table I. Pretreatment features and response to bleomycin and bleomycin-mitomycin C therapy.

Pat no.	Age (yrs)	Histology	Clinical stage FIGO TNM	Prior treatment*	Duration of remission after 1st treatment (mos)	Recurrence Primary tumour Distant metastases	Total dose (mg) of Bleomycin Mitomycin C	Response	Duration (mos) of Remission	Survival
Bleomycin alone										
1	68	Well-diff	I	T ₁ N ₁ M ₀ Op + RT	216	+	-	300	CR	24+
2	78	Well-diff	IV	T ₃ N ₂ M ₀ Op + RT	7	+	-	170	CR	4
3	81	Moderate diff	IV	T ₃ N ₁ M ₀ Op + RT	7	+	-	285	PR	3
4	63	Moderate diff	IV	T ₃ N ₂ M ₀ Op + RT	1	+	Pelvis	150	PR	2
5	70	Well-diff	III	T ₂ N ₂ M ₀ Op + RT	-	+	Inguinal nodes	300	PR	2
6	68	Well-diff	IV	T ₄ N ₂ M ₀ RT	-	+	Pelvis	300	SD	4
7	43	Well-diff	I	T ₁ N ₀ M ₀ Op + RT	12	-	Pelvis Skeleton	105	PD	-
8	70	Well-diff	I	T ₁ N ₁ M ₀ Op + RT	96	+	Pulmonary	180	PD	-
9	62	Well-diff	IV	T ₄ N ₁ M ₀ Op + RT	8	+	Pelvis Inguinal nodes	180	PD	-
10	52	Moderate diff	I	T ₁ N ₁ M ₀ Op + RT	3	-	Pulmonary Ribs	45	PD	-
11	68	Moderate diff	I	T ₁ N ₁ M ₀ Op + RT	11	-	Inguinal nodes	180	PD	-
Bleomycin-mitomycin C combination										
12	70	Well-diff	III	T ₁ N ₂ M ₀ Op + RT	6	-	Pelvis	175	CR	7+
13	70	Well-diff	III	T ₃ N ₂ M ₀ Op + RT	10	+	-	175	PR	7+
14	78	Moderate diff	III	T ₃ N ₂ M ₀ -	-	-	-	175	PR	3+
15	71	Low diff	IV	T ₄ N ₁ M ₀ -	-	-	-	140	PR	2+
16	70	Well-diff	IV	T ₃ N ₂ M ₁ RT	-	+	Inguinal nodes	175	PR	3
17	77	Well-diff	III	T ₂ N ₁ M ₀ Op + RT	6	-	Inguinal nodes	105	SD	3
18	70	Well-diff	II	T ₂ N ₀ M ₀ Op + RT	132	+	-	175	SD	8
19	70	Moderate diff	IV	T ₃ N ₂ M ₀ Op + RT	-	+	Inguinal nodes	70	PD	3
20	49	Moderate diff	I	T ₁ N ₀ M ₀ Op + RT	2	+	-	175	PD	-

*Op = vulvectomy + superficial inguinal lymphadenectomy; RT = radiotherapy of the inguinal lymph nodes (¹³⁷Cs, peak-absorbed dose = 21 Gy).

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Acta Radiologica (Accepted for publication)

TREATMENT OF RECURRENT SQUAMOUS CELL CARCINOMA OF THE VULVA

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SUMMARY

Continuous follow-up of 244 patients treated for primary invasive squamous cell carcinoma of the vulva during a 20-year period (1960-1979) resulted in the detection of recurrent (or persistent) disease in 60 (25 %) cases.

Nineteen (8 %) presented with tumour progression during the primary treatment or within the following six months. These patients have not been adequately treated with the primary treatment technique. Forty-one (17 %) presented with local and/or regional treatment failures later than six months following treatment. Twenty-nine had local recurrences, nine regional metastases and three local recurrences and regional metastases.

The treatment technique for central recurrences has been surgery, in a few cases combined with radiotherapy and chemotherapy. In approximately one-third of the cases, this treatment has resulted in long-term or permanent cure. The median survival time was three years.

The prognosis is often extremely poor in cases of regional metastases. Treatment, however, normally gives good palliation although of short duration. The median survival time was six months.

INTRODUCTION

The traditional treatment of invasive carcinoma of the vulva during the last 30 years has in most centres been radical vulvectomy and groin lymphadenectomy, sometimes combined with pelvic lymphadenectomy and/or radiation treatment of the lymph node stations.

This aggressive therapy has resulted in well-documented, (Brunschwig & Brockunier 1967, Green 1978, Taussig 1940, Way 1960) good survival rates. Increased aggressiveness also severely increases the complication risks, which is also a well-documented fact (Calame 1980, Green 1978, Way 1960). Reports during recent years have, however, shown lower complication frequencies with modified surgery, without any concurrent impairment of the survival rate (Abitbol 1973, Green 1978, Morley 1976).

Despite aggressive therapy, a recurrence rate of 20-30 % (Abitbol 1973, Acosta et coll. 1978, House & Hester 1968) is not uncommon. Few reports have been published in the literature regarding the treatment of local and regional treatment failures (Buchler et coll. 1979, Podrats et coll. 1982).

In spite of their high median age, this group of patients normally tolerate the treatment for recurrent disease. Since carcinoma of the vulva, furthermore, is often a slow-growing malignancy, which remains localized to the vulvar-perineal region or the groins for several months without distant metastasizing, the treatment of local recurrences and regional metastases is of interest. This paper deals with these problems.

MATERIAL AND METHODS

During 1960-1979, 244 patients with squamous cell carcinoma of the vulva in stages I-IV, were given treatment with curative intention. This has consisted of vulvectomy, in some cases supplemented with groin dissection and pelvic lymphadenectomy. Preoperative radiotherapy to the groins has been administered, and in cases with tumour in extirpated lymph nodes, postoperative radiotherapy has also been given. Patients not operated with lymphadenectomy received groin radiotherapy as the sole treatment given to these regions. These primary treatment techniques have earlier been described in detail (Simonsen 1983).

Treatment failures registered in the perineum, the vulva, the lower half of the vagina or in the urethra have been classified as local recurrences. Metastases to the groin and/or pelvic walls after completion of treatment have been defined as regional metastases.

In 60 patients, local and/or regional treatment failures were registered.

Nineteen (15 stages III-IV; 4 stages I-II) of these patients presented with tumour progression during the primary treatment or within the following six months. Three out of four stages I-II tumours were not radically operated upon and had metastases in excised lymph nodes. These nineteen patients represented problems arising from the primary treatment techniques. None of these patients were alive three years after primary treatment.

The remaining 41 patients with local and/or regional treatment failures constitute the basis for this report. The type of treatment failure and the treatment given to the primary lesion are shown in Table I.

The treatment technique described below concerns the first treatment failure. The use of second-line procedures, as the treatment of generalized disease, is not dealt with.

Table I. Primary treatment technique and type of treatment failure in 41 patients.

Type of treatment failure	Primary treatment				Total
	Hemivulvectomy	Vulvectomy	Vulvectomy and groin diss	Vulvectomy, groin diss and pelvic lymphadenectomy	
Local recurrences	2	11	12	4	29
Regional metastases	-	5	4	-	9
Local recurrences and regional metastases	-	2	1	-	3
Total	2	18	17	4	41

The distribution of the tumour size for the group of 32 patients with primary local recurrences was T_1 ~16, T_2 ~13 and T_3 ~3. In the whole group of 244 patients given treatment with curative intention, the corresponding figures were T_1 ~99, T_2 ~96, T_3 ~44 and T_4 ~5.

Surgical radicality of the primary vulvectomy for the group of 32 patients was: radical ~19, not radical ~8, doubtfully radical ~5. In the whole group, the figures were 161, 39 and 44, respectively. Surgery has been used for central recurrences, from wide local excision to re-vulvectomy using the warm knife open-wound technique (Simonsen et coll. 1982). This technique has been performed in 30 out of 32 patients. One patient was only given radiotherapy and one patient received both radiotherapy and chemotherapy. In three of the 30 cases, anorectal resection and colostomy was also performed. In five of these 30 patients, preoperative radiotherapy was given. In one patient postoperative chemotherapy was given.

Radiotherapy to the vulva was given about three weeks preoperatively, as a rule using 15-25 MeV e^- , depending on the calculated depth of the tumour infiltration: 4.5-7 cm. Single-field technique was used and a peak absorbed dose of 3.0 Gy per fraction, three fractions/week to a total of 30-45 Gy. This will give a target absorbed dose (specification point on the central axis at the centre of the target area) of about 27 Gy and 40.5 Gy respectively. CRE-value 12.6 and 16.0 respectively.

Radiotherapy as the sole treatment of local recurrence, or in combination with chemotherapy, was given using the same technique as described above up to a total absorbed dose of about 45 Gy - 54 Gy. CRE-value 16.0 and 18.0, respectively.

The chemotherapy used was bleomycin or bleomycin in combination with mitomycin C. The bleomycin regimen used was 15 mg i.m. twice a week up to a total dose of ≤ 300 mg. The combination bleomycin-mitomycin C regimen used was: bleomycin 5 mg i.v. during 6-8 hours on days 1-7 and mitomycin C 10 mg i.v. on day 8 as a bolus dose. This dose schedule was given as one course repeated four times, with a 1-week recession period between each course.

In the group of 244 patients, groin dissection was performed in 122, of whom 62 had tumours in the operative specimens.

Seven out of twelve patients with regional metastases were primarily only given radiotherapy to the groins.

One of five patients who primarily had received groin lymphadenectomy had tumour in the surgical specimens.

Among the twelve patients with regional metastases, three also had local recurrences. Re-vulvectomy and groin dissection (one pelvic lymphadenectomy) were performed in these patients.

Groin dissection was performed in three patients with only regional metastases.

Three patients received only radiotherapy and three others had a combination of radiotherapy and chemotherapy. Postoperative radiotherapy was given to four patients after groin dissection. The postoperative radiotherapy to the groins was as a rule given using a ^{60}Co -unit with single-field technique and SSD 80 cm, and a field size of about 150 cm^2 . The peak absorbed dose was 3 Gy per fraction, five fractions/week, up to a total of 20-40 Gy. The same dose was given in cases treated only with radiotherapy or with combined radiotherapy and chemotherapy. The deepest part of the target, representing the inguinal lymph nodes (operation area) and the external and interiliac lymph nodes, was assumed to be located 10 cm from the skin surface. This will give a target absorbed dose (specification point on the central axis at the centre of the target area) of about 18 Gy to 36 Gy.

Chemotherapy consisted of bleomycin or bleomycin in combination with mitomycin C, as described earlier in this report.

The prognosis was defined using the life-table analysis and the median survival time from completion of treatment of recurrence and metastasis.

Survival rate, %

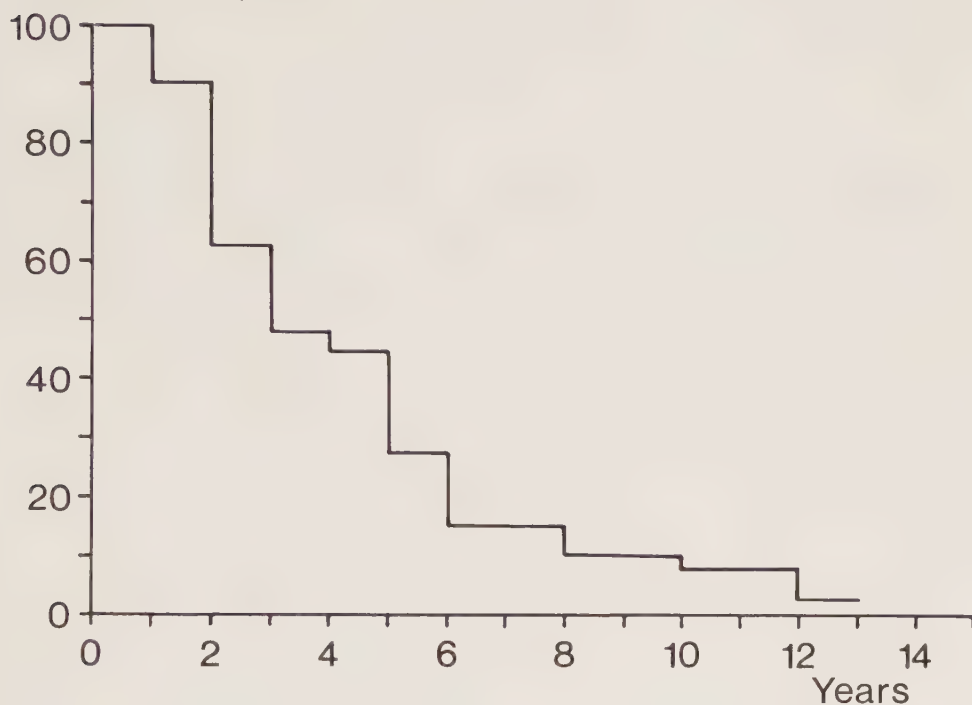


Fig 1. Median survival for patients with local recurrences from completion of treatment of recurrence is 3 years.

RESULTS

The survival rate for patients with local recurrences using the life-table technique is shown in Fig 1. Eleven patients were still alive after 2-17 years, with no evidence of disease.

Two patients treated only with radiotherapy and chemotherapy, died from cancer within six months. The median survival time was three years.

Only one out of twelve patients with regional metastases was still alive with no evidence of disease after six years. She was treated with surgery and postoperative radiotherapy to the groins. Eleven patients died from cancer within 0.1-3.5 years. The median survival time was six months.

Complications

The complication rate in connection with treatment for recurrence was insignificant. Wound infection of short duration in connection with vulvar surgery performed without primary closure is normal and easily cured (Simonsen et coll. 1982). Vaginal stricture in connection with repeated vulvar surgery is a frequent complication. Plastic surgery was, however, necessary in only two cases. Following reoperation of the clitoris/urethral region, extirpation of the distal urethrae was often performed, which frequently results in transient incontinence problems. Only one patient developed persistent incontinence. In three cases with tumour progression in the anal region, colostomy has been performed.

DISCUSSION

Even with an aggressive primary treatment, recurrences and regional metastases occur in 20-30 % of patients with vulvar carcinoma.

The figures for the size of the tumour and the radicality of the primary vulvectomy were the same in patients with local treatment failures as in the whole group (244 patients). The reason for this is that patients with aggressive tumours and with tumours which on account of localization and primary extension have proved difficult to treat as a rule have much faster progression of their disease (within six months). The distribution of tumour size for this group of 19 patients was as follows: T₁=2, T₂=2, T₃=11 and T₄=4. Radicality of vulvectomy was as follows: five radical, nine not radical and four of dubious radicality. In these cases, the treatment of the regional lymph node stations has, moreover, been very difficult.

With regard to the regional treatment failures that appear more than six months after termination of primary treatment, a greater number of regional metastases were registered in the group of patients who did not receive lymphadenectomy. The difference was not, however, significant, and the material is small. Tumour in extirpated lymph nodes was observed in only one patient at the time of the primary operation. It was not possible to deter-

mine if the observed regional metastases among patients given lymphadenectomy were the result of progressive tumour growth from non-treated or inadequately treated iliacal lymph nodes.

The treatment of local and regional treatment failures represents a difficult problem. With regard to local recurrence, curative results may be expected in many cases. In the case of regional metastases, curative treatment is seldom achieved. Treatment of local recurrence and regional metastases, although of short duration, normally gives good palliation, however.

CONCLUSIONS

The treatment of local recurrence of carcinoma of the vulva is preferably surgical, possibly combined with preoperative or postoperative irradiation. In approximately one-third of the cases, this treatment results in long-term palliation or permanent cure.

In case of regional metastases, the prognosis is extremely poor. Long-term survival can be expected in very few cases, even if groin dissection and pelvic lymphadenectomy combined with irradiation are possible to perform.

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